COLPOSCOPIC EVALUATION OF UNHEALTHY CERVIX AND ITS CORRELATION WITH PAP SMEAR AND BIOPSY

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CERTIFICATE

This is to certify that the dissertation entitled **" Colposcopic Evaluation of Unhealthy Cervix and its correlation with PAP smear and Biopsy"** *submitted by* ***Dr. R.Vinotha*** *to the Faculty of Obstetrics and Gynaecology, The Tamilnadu Dr. M.G.R. Medical university, Chennai in partial fulfillment of the requirement for the award of M.D. Degree Branch II (Obstetrics and Gynaecology) is a bonafide research work carried out by her during the period of April 2004 to June 2005 under our direct supervision and guidance.*

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CONTENTS

INTRODUCTION

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Cancer cervix continues to be the most common genital cancer encountered in India accounting for 80% of all female genital cancers (Shaw).

The concept pre-invasive disease of cervix, which denotes changes that are confined to the cervical epithelial cells was introduced in 1947. Early detection of pre invasive disease and treatment of CIN has the potential to improve the outcome of patients.

Invasive cancer of cervix is considered to be a preventable condition, since it is associated with a long pre-invasive stage (CIN), making it amenable to screening and treatment.

Colposcopy of cervix is usually classified as

1. Routine Colposcopy
2. Screening Colposcopy
3. Selective Colposcopy

1. Routine Colposcopy

It is done as a part of all gynaecological examinations. But this is not possible in government hospitals as a hurried examination can result in poor standards.

2. Screening Colposcopy

Here colposcopy is incorporated while screening for cancer cervix, keeping in

mind, the high false negative rate of pap smear for screening for SIL and CA cervix.

3. Selective Colposcopy

Here Colposcopy is performed only when indicated. Indications are :-

- Evaluation of the women with abnormalities on pap smear, with no gross lesion on the cervix or vagina.
- Persistence of inflammatory cells despite adequate treatment.
- Naked eye examination reveals an "unhealthy cervix" suspicious of malignancy, especially one with significant aceto whitening after acetic acid wash.
- Women with post coital bleeding, metrorrhagia and post menopausal bleeding.
- To study the site and extension of lesion in the cervix and to do directed biopsy.
- Enables ablation and excision of CIN wherever possible.
- Monitoring of women with anogenital condylomas.

Hence, Colposcopy helps in evaluation, treatment, assessment of progress and follow up of cases.

AIM OF THE STUDY

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1. To screen women who have abnormal symptoms with pap smear and Colposcopy.

2. To screen women who have unhealthy cervix on visual inspection and women with dysplastic smears with Colposcopy.

3. To do histopathological analysis of colposcopically directed biopsies.

4. To compare and correlate Colposcopy and cytology with histopathology.

5. To critically evaluate the sensitivity and specificity of Colposcopy versus pap smear in the early detection of dysplasias.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

History of Colposcopy

Hinselman from Germany in 1925, using a front lamp together with a Leitz magnifying glass, invented Colposcopy and conducted studies on vulva, vagina and cervix, initiating the first Colposcopy clinic.

Walter Schiller in 1928, invented Schiller's test. He found that weak iodine solution would stain the glycogen in normal cervical squamous epithelium and result in dark mahogany colour while leaving areas of cancer unstained.

Sacks in 1934 complained that this cumbersome equipment leads to non-acceptance of this method.

Papanicolaou and Trait in 1943, published their book on cancer diagnosis by vaginal smear.

Ayre in 1947, introduced spatula for sampling the cervix.

Hinselmann in 1956, experimented with video Colposcopy.

Navrratil indicated that by combination of cytology with Colposcopy, it was possible to increase the accuracy of early carcinoma detection by 99%.

Richart in 1967, introduced the term cervical intraepithelial neoplasia. Coppleson and Reid in 1967, described colposcopic features of immature metaplasia.

In 1970, Stafl developed colposcopic terminologies.

In 1971, British colposcopic group was formed. Coppleson, Pixely and Reid published their first edition of colposcopic text and established the importance of transformation zone.

In 1975, IFCPC standardized the colposcopic terminologies and introduced international nomenclature for colposcopic findings causing rapid adoption of Colposcopy world wide.

In 1984, Evaluation of cervical lesions by the combined use of cytology, Colposcopy and biopsy by Usha Saraiya and Maya Lulla at their Colposcopy clinic at Mumbai showed pick up rate of CA cervix in Colposcopy alone was 13% in non – suspicious group.

Duggan et al in 1988, studied the natural history of CIN I lesions.

In 1990, De palo (Italy) published a manual on Colposcopy and treatment of lower genital disease.

In 1993, Simmons, evaluated the role of smoking as a cause for cancer cervix, suggesting biochemical evidence with smoking modified the DNA in cervical epithelial cells leading to the development of cancer cervix.

In 1997, Gullota, Margarati and Rabihi examined the correlation among Colposcopy, cytology and HPE in the diagnosis of intraepithelial lesions of cervix. Sensitivity for detection of CIN was 70% with cytology and 92% with Colposcopy.

Mitchel et al in 1998, did a meta analysis in the role of Colposcopy for the diagnosis of CIN and found that average weighed sensitivity of diagnostic Colposcopy with all grade cervical dysplasias was 96% and average weighed specificity was 48%.

Feinstein et al in 1988, evaluated the pre and post operative value of endocervical curettage (ECC) in the detection of CIN and invasive cancer and concluded that routine ECC should be a part of pre operative assessment of an abnormal pap smear but may be

unnecessary in the evaluation for residual dysplasia.

Belinson et al, studied CA cervix screening by simple visual inspection with acetic acid and concluded that it was cost effective.

Cullimore, reviewed cytological reporting of abnormal glandular cells on cervical smears in order to assess the predictive value of these reports and the contribution of Colposcopy in the assessment of these abnormalities.

Maiman et al in 1998, studied the prevalence, risk factors and the accuracy of cytologic screening for CIN in women with HIV and found that there was a high prevalence of abnormal cytology in CIN in HIV infected women.

Shalini et al, studied the cytologic, colposcopic and histopathological evaluation in patients with post coital bleeding and the sensitivity and specificity of cytology was found to be 56% and 90% respectively.

Ferrero et al, in their study found that all HIV infected women, independently from their immunological and clinical conditions, need regular pap smears with appropriate follow up for abnormal cervical cytology and that could prevent nearly all deaths from cervical cancer.

Olaniyan B., explained the validity of Colposcopy in the diagnosis of early cervical cancer and concluded that Colposcopy is a valid tool for the diagnosis of CIN. Its integral role in the management of early cervical cancer was justified.

Jin L. Wan Y et al, evaluated new cytologic screening methods like papnet cytology, computer technology and thinprep pap test (TPT) on CIN and concluded that women ranging from 30-50 years should receive cytologic screening and colposcopic examination regularly.

Basu P.S and Sankaranarayan et al, studied the characteristics of VIA with 4% acetic acid and VILI in cancer cervix screening and estimated the sensitivity of VIA and VIAM to detect CIN 2-3 lesions were 55.7% and 60.7% respectively.

Etherington used video tele colposcopy to record colposcopic findings, which were subsequently transmitted to a specialist for interpretation. The sensitivity was found to be 88.9% and specificity was 93.3%.

Yarandi and colleagues studied the colposcopic and histologic findings in women with a cytologic diagnosis of ASCUS and concluded that ASCUS was a good marker for detecting SIL and condyloma.

Brown B-H et al, compared the cervical impedance spectrometry in the cervical epithelium of women with CIN and normal epithelium and concluded that it provided a potentially promising screening tool with similar sensitivity and specificity to currently used screening tests, but with potential advantage of providing instant results.

Benedict J.L. did an analysis on 84244 patients from British Columbia by cytology and Colposcopy program and found that Colposcopy correlated with referral cytology within one degree in over 90% of cases and cytology histology correlation within one degree occurred in 82%.

CIN

CIN

The incidence of cervical dysplasia is reported to be 15:1000 in women who were cytologically screened. The incidence of severe dysplasia is reported to be 5:1000 according to ICMR studies (Shaw).

Age adjusted incidence rates for invasive cancer ranges from 19-44/100,000 women in various cancer registries in India. Highest incidence is noted in Chennai – 43.5/100,000.

The cumulative risk of CA cervix is 1.58% in Mumbai and 3.6% in Chennai. In other words, 1 in 62 woman in Mumbai and 1 in 28 woman in Chennai may develop cancer cervix in their life. (ICMR – 1992)

Etiology and Risk Factors

1. Marriage and Sexual Behaviour

Increased risks are associated with coitus at an early age, coitus with multiple sex partner, and coitus with high risk men (Miller et al – 1976, Canadian Task Force – 1982).

2. Local Hygiene

Cancer cervix is found to be positively associated with lack of daily genital washing and negatively with the use of clean sanitary napkins during menstruation (Zhang et al – 1989).

3. Contraception

Barrier methods may be protective while OCP increases the risk of CIN and invasive cancer which is attributed to the hormonal changes produced in the cervical epithelium (Beral et al 1988).

4. Dietary factors

Deficiency of Vitamin A, C, E and Folic acid are related to cancer cervix and dietary supplementation of these vitamins may prevent its occurrence (Verreault – 1989).

5. Smoking and Douching

Smoking and douching with tar substances may have a role in CIN. (Winkelstein et al 1991). Smoking more than 20 cigarettes per day had increased the relative risk to get CIN and invasive cancer (Nunez et al – 2002).

6. STD

There is a definitive association of Human Papilloma Virus (HPV) – 16,18,31,33 with CIN. HPV – 16 is associated with CIN. HPV – 16 is associated with High grade squamous cell carcinoma and HPV-18 is associated with adenocarcinoma. HPV – 31,33,35 are associated with intermediate oncogenicity (Crum et al – 1985, Levine et al – 1984).

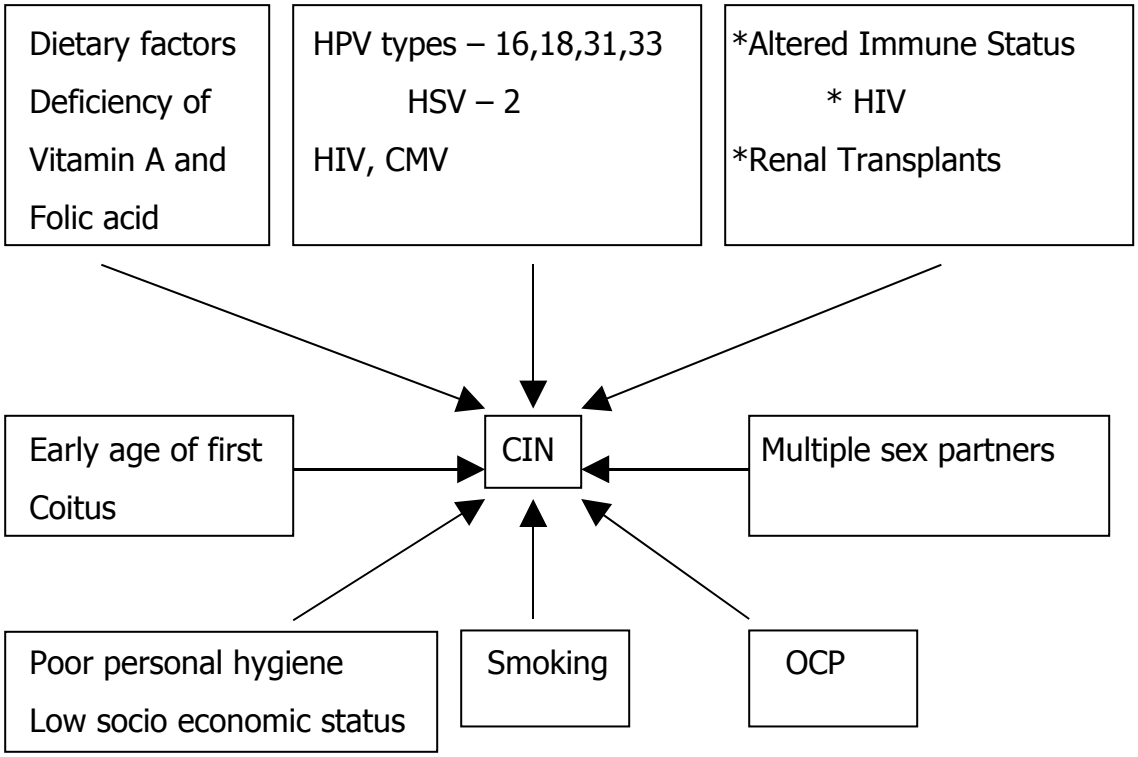
Increased risk of cervical cancer has been reported with either STD infections like HSV-2, HIV and CMV. This risk is found to increase significantly with increase in the number of different organisms (Schmauz et al – 1989).

7. Immuno suppression

Both pre – invasive and invasive lesions are more prevalent in chronically immuno compromised woman, eg. In HIV (Maiman et al – 1998) and in renal transplants (Alloub et al – 1988) and (Mayerson et al – 1991).

8. Parity

Although multiparity is associated with increased incidence of CA cervix, there is no significant evidence to prove it (Cramer – 1986).



Natural history of CIN

Original squamous epithelium is derived from the urogenital sinus epithelium and starts at the vulvovaginal line, lines the vagina, covers the major portion of the portio of cervix and abuts upon the columnar epithelium to form the original squamo columnar junction.

Under low vaginal acidity, the reserve cells proliferate, lifting the columnar epithelium. There is centripetal growth of original squamous epithelium growing beneath the columnar epithelial cells. Process of squamous metaplasia begins in the line of the columnar villi which are first exposed to vaginal acidity.

A new squamo columnar junction is continuously formed that gradually replaces the native columnar epithelium. The deeper clefts, however, may not be completely replaced by the metaplastic epithelium resulting in the formation of Nabothian cysts. Gland openings and nabothian cysts mark the original SCJ and the outer edge of the original TZ. The area between original SCJ and the new SCJ is referred to as Transformation Zone (TZ).

Physiological transition occur during three phases of life.

1. Fetal
2. Menarche
3. First pregnancy

Anatomy of Transformation zone

Proximal border of TZ is the upper limit of squamous metaplasia where the immature squamous metaplasia abuts a circumferential ring of unaltered columnar epithelium.

Original squamocolumnar junction has 4 layers.

1. **Basal layer** : Single row of immature cells with large nuclei and small cytoplasm.

2. **Parabasal layer** : Two to four rows of cells that have normal mitotic figures.

3. **Intermediate layer** : Includes four to six rows of cells with large amount of cytoplasm in a polyhedral shape, separated by intercellular space.

4. **Superficial layer** : Includes five to eight rows of cells with small uniform

pyknotic nuclei and acidophilic cytoplasm filled with glycogen. These cells exfoliate and form the base for pap smear.

Columnar epithelium

Single layer of columnar cells with mucus at the top and a round nucleus at the base.

Metaplastic epithelium

Transformation from columnar epithelium to squamous epithelium is known as metaplasia to the histologists and as TZ to the colposcopists. This is the area of development of neoplasia and the area of interest to the colposcopists. Its caudal limit is the original SCJ and its cephalic limit is the new SCJ.

Pathogenesis of CIN

In most cases, CIN is believed to originate as a single focus in the TZ at the advancing SCJ. The anterior lip of cervix is twice as likely to develop CIN as the posterior lip and CIN rarely originates in the lateral wall.

Once CIN occurs, it can progress horizontally to involve the entire TZ, but usually does not replace the original squamous epithelium. Proximally CIN involves the cervical clefts and this area tends to have more severe lesions.

CIN is most likely to begin either during menarche or after first pregnancy when metaplasia is more active. Conversely, a woman who has reached menopause without developing CIN has little metaplasia and is at a lower risk.

Progression and Regression of CIN

The spontaneous regression rate of biopsy proven CIN I is 60-85% in prospective studies. This regression typically occurs within a 2 year follow up with cytology and Colposcopy.

This information had led to the recommendation that patients who have biopsy diagnosis of CIN I with satisfactory Colposcopy and who agree to the evaluation every 6 months can be treated by observation. If the lesion progresses in follow up or persistent after 2 years, ablation is recommended (Novak's gynaecology).

CIN II and CIN III require treatment. This is based on meta analysis showing that CIN II progresses to CIS in 22% of cases and to invasion in 5%.

CIN I	Regress	Persist	Progress to CIN III	Progress to invasive CA
CIN I	57%	32%	11%	1%
CIN II	43%	35%	22%	5%
CIN III	32%	56%	-	>12%

(From Ostor AG. Inter J. Gynaecol pathology 1993;12)

HPV and CIN

The cytologic changes in HPV were first recognized by Koss and Durfee in 1956 and was given the name "Koilocytosis". Epidemiological studies suggest that HPV is associated with a 10 fold or greater risk of cervical neoplasia than controls (Schiffman et al 1992).

The HPV genome has been demonstrated in all grades of CIN. Portions of HPV DNA becomes integrated into the host cell. Malignant transformation requires expression of E_6 and E_7 glycoproteins produced by HPV which are diagnosed in the transected cell lines – SiHa, HeLa, Caski.

IARC – International Society for Research on Cancer has classified HPV types 16 and 18 as Carcinogens in humans. Genital HPV types now exceed 20, only certain types account for CIN – HPV 16,18,31,33,35,39,51,52,56 and 58.

HPV 16 - is found in 47% of CIN II and III

HPV 18 - is found in 23% of invasive CA

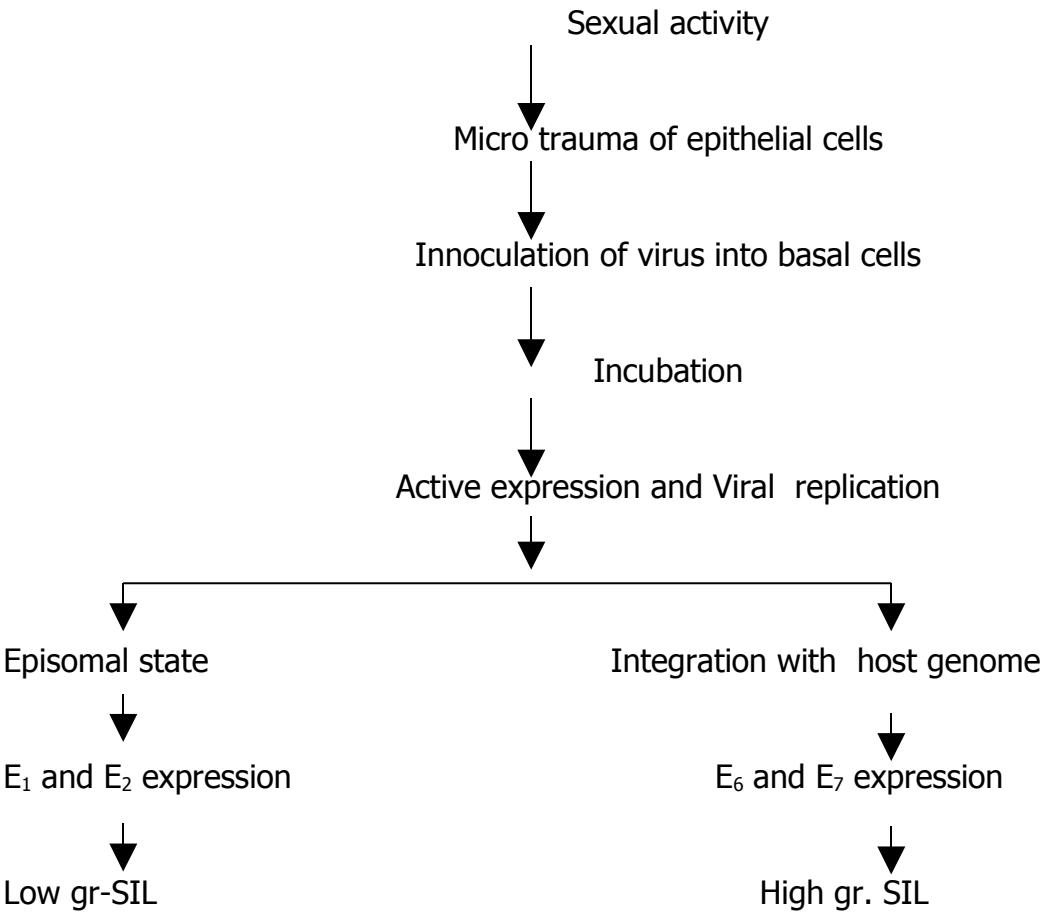
5% of women with CIN II and III

5% of women with CIN I and

$\leq$ 2 % of women with negative findings

(Novak's gynaecology)

Usually HPV DNA does not persist. The infection is eventually suppressed. A minority of women develop persistent infection that may progress to CIN. Factors that may have a role in this progression include smoking, OCP Usage, infection and STD which cause integration of HPV DNA into human genome.


Sexual activity
Micro trauma of epithelial cells
Innoculation of virus into basal cells
Incubation
Active expression and Viral replication
Episomal state
Integration with host genome
E_1 and E_2 expression
E_6 and E_7 expression
Low gr-SIL
High gr. SIL

Screening Procedures for CIN

Screening Procedures for CIN

The various screening procedures used to detect CIN are :-

1. Pap Smear
2. Colposcopy
3. Cervicography
4. Speculoscopy, VIA, VIAM, VILI
5. HPV DNA detection and typing
6. Polarprobe (Truscan)
7. Spectroscopy

1. Pap Smear

The pap smear initially described by papanicolaou and Tract is used to detect exfoliative cells from the cervix that may be precancerous or cancerous.

Conventional Pap Smear

According to American Cancer Society, ideal time to take pap smear is 5 days after menstruation. The patient should be instructed not to use a vaginal douche or any type of lubricant or spermicide for 24 hours prior to having a cytologic specimen obtained. The ectocervix and the area of vagina adjacent to the cervix must be fully visible when smear is obtained. The patient should not bleed and should not have marked vaginal infection. The infection must be treated accordingly and patient must be rescheduled for pap smear during next cycle.

The smear is taken with Ayre's spatula or with moistened brush around the external os by making 360^0 rotation with minimal pressure and smeared and fixed in a glass slide with

95% alcohol. Staining done with papanicolaou staining procedure which employ,

- Haemotoxylin as a nuclear stain and
- Orange G – 6 and Eosin alcohol (Ea-36) as cytoplasmic counterstains. The slides are finally mounted in Canada balsam and examined and interpreted.

Various forms of Interpretations

Papanicolaou (1943)	Richart	WHO (1975)
Gr I – Normal cells	Normal	Negative for cancer
Gr II – Slightly abnormal, suggestive of inflammatory changes. Repeat smear after treating infection	Negative	Atypical squamous cells
Gr III – More serious type usually indicative of biopsy	CIN I	Mild dysplasia
Gr IV – Distinctly abnormal and definitively require biopsy	CIN II CIN III	Moderate and severe dysplasia
Gr V – SCC	SCC	SCC

Bethesda classification (2001)

Non neoplastic – negative for intraepithelial lesion or malignancy.

Organisms

- Trichomonas vaginalis
- Candida species
- Shift in vaginal flora suggestive of bacterial vaginosis
- Bacteria morphologically consistent with actinomycoces species
- Cellular changes associated with HSV

Non neoplastic findings

Reactive cellular changes associated with

- Inflammation
- Radiation
- IUD

Epithelial cell Abnormalities

Squamous cell

- Atypical squamous cells
  - ASCUS
  - ASC-H
- LSIL – encompassing HPV / mild dysplasia / CIN I
- HSIL – encompassing moderate and severe dysplasia / CIN II and CIN III
  - With features suspicious of infection
- Squamous cell carcinoma

Glandular cell abnormalities

- Atypical
- Endocervical cells
- Glandular cells
- Atypical glandular / endocervical cells,favour neoplasia
- Endocervical adenocarcinoma in situ
- Adenocarcinoma – Endocervical / Endometrial / Extra uterine
- Not otherwise specified

Other malignant neoplasms

Specify

Newer methods of cytodiagnosis

1. **Liquid based cytology** – Thinprep, Cytorich

Advantages are

- Removes most mucus, protein and fresh blood from the preparation.
- Transfers 80-90% of cells to the slide as compared to 10-20% with conventional tests.
- Distributes cells uniformly
- Improves fixation
- Preserves cellular architecture

2. **Automated cytologic screening** – papnet, auto pap 3000c

They are approved only for rescreening the previously manually screened smears to identify false negative smears. Reduces false negative by 32%.

3. **Colposcopy**

Basically, a colposcope is composed of a single or double main objectives lens, a magnification changer, binocular tubes with prism, eyepieces, diopter adjustment and a green filter to study blood vessel patterns.

Working distances < 20 cm is too short and > 30 cm is too long. Usual focal length used is 300mm. High magnification is used for microscopic study of lesions and low magnifications are often necessary during laser or LEEP treatment so as to visualise the entire surgical field. To visualise the entire lesion, a magnification of 10X or less is required. The diameter of normal cervix varies between 3-6cm. To see the

entire cervix requires a magnification of 3.5 to 5.5 times. To see the adjacent viscera, lesser magnification are used.

Various speculums are used. Graves speculum is used for LEEP Miller speculum is used to improve visualization of side walls and Pederson speculum used in women with narrow vagina. Cusco's self retaining bivalve speculum is also used.

Various biopsy forceps used are, the Kevorkian forceps, Tischler Morgan forceps, Minitownsend forceps to obtain smaller specimens. Routine punch biopsy forceps is also used. Curettes for obtaining endocervical specimens are Kevorkian, Novak's and Randall's curettes.

Colposcopic Technique

Favourable period for colposcopic examination is 8-10th day of a cycle as the external os is widely open during this time and abundance of watery secretions serves as a good refractory medium and facilitates examination of endocervix.

If the upper limit of TZ is not visible, the examination may be rescheduled and the patient is instructed to take Ethinyl estradiol 50 μg/dly/5-7 days prior to examination which causes canal dilatation. In 15%, unsatisfactory colposcopic findings are seen, where endocervical curettings are taken.

2002, International Federation of cervical pathology and Colposcopy (IFCPC) devised new colposcopic terminology (Barcelona).

1. Normal colposcopic findings

a. Original squamous epithelium
b. Columnar epithelium
c. Normal TZ

2. Abnormal Colposcopic findings

a. Within the TZ

- Acetowhite epithelium
  - Flat
  - Micropapillary, dense
- Punctation
  - Fine
  - Coarse
- Mosaic
  - Fine
  - Coarse
- Iodine partial positivity
- Iodine negative epithelium
- Atypical vessels

b. Outside the TZ

- Acetowhite epithelium
  - Flat
  - Micropapillary, dense
- Punctation
  - Fine
  - Coarse
- Mosaic
  - Fine
  - Coarse

- Iodine partial positivity
- Iodine negative epithelium
- Atypical vessels

c. Colposcopically suspect invasive carcinoma

d. Unsatisfactory Colposcopy

a. Squamocolumnar junction invisible
b. Severe inflammation or atrophy
c. Cervix not visible

e. Miscellaneous findings

a. Exophytic condyloma, Keratosis (Leucoplakia)
b. Inflammation
c. Atrophy
d. Ulcer, Erosion
e. Deciduosis
f. Polyps

Normal Colposcopic findings

1. Original squamous epithelium

Smooth, pink, uniform, featureless epithelium without columnar remnants. The vascular patterns are hairpin capillaries and network capillaries. In Trichomonas vaginalis, double capillaries with two or more crests at the top will be seen as forklike.

2. Columnar epithelium

Irregular surface with atypical grapelike or villus appearance. Each Villus contains fine capillary that is visualised with saline. Under high magnification colour appears reddish because of underlying stromal vessels.

3. Normal Transformation zone

Area between the original SCJ and new SCJ in which metaplastic epithelium has replaced the pre existing columnar epithelium. Coppleson and Reid in 1967, described the features of immature metaplasia in three stages after acetic acid application.

Stage I Individual villi assume opaque white appearance.

Stage II Individual villi retain their density, but fuse so that intervening spaces are filled in

Stage III Villus configuration is lost and the new epithelium has a homogenous ground glass pattern.

Care should be taken, not to configure this immature metaplasia with dysplasias. Components of TZ are :-

1. **Branching vessels** – Large capillaries showing tree like branching pattern found only in TZ in the walls of retention cysts.
2. **Nabothian follicles** – Mucus filled retention cysts.
3. **Gland openings** – Small holes from which mucus seems to pour, representing areas where the new squamous epithelium has covered incompletely and underlying columnar cleft is in continuity with the surface.

Abnormal colposcopic findings

CIN tend to be confined to the TZ. On contrast, subclinical papilloma virus infection (SPI) is not so limited and may involve the TZ, the original SCJ and sometimes further extend caudally to involve vagina and cranially to involve the columnar epithelium SPI beyond TZ suggests absence of CIN.

1. Aceto white epithelium

It is a focal abnormal lesion seen after application of 5% acetic acid. The white epithelium is a transient phenomena that is seen in areas of increased nuclear density either flat or micropapillary. Dense and more opaque lesion signifies CIN. Acetic acid causes agglutination of cervical mucus facilitating its removal and also removes vaginal discharge, causes coagulation of epithelial proteins. Effect takes a minimum of 10-30 secs to develop and it fades away in 30-40 secs.

Flat AW

Areas of high nuclear activity appear white. A milder degree of AW occurs in areas of immature metaplasia.

Dense AW

A severe lesion is associated with dense AW changes that appears fast and persists longer. Dense AW change within columnar epithelium may indicate glandular change.

2. Punctation

Presence of fine stippling produced by the terminal end of intra epithelial capillaries closely spaced with gridlike patterns. In severe punctations, there is an increase in vessel caliber and spacing. Fine punctations indicate a milder lesion and severe lesion is indicated by a coarser punctation.

3. Mosaic pattern

Fine vessels that form partitions between blocks of AW epithelium, often regular in size and shape. Higher grades display coarser patterns and vessels with increased intercapillary distance.

4. Iodine negative epithelium

They represent columnar epithelium, immature metaplasia, atrophy, inflammation, HPV infection, CIN and SIL.

Partial iodine uptake shows a speckled appearance in an area of slight AW change and it may be due to immature metaplasia, regenerating epithelium, SPI, low grade CIN. An yellowish area within an area of dense AW is highly suggestive of high gr. CIN.

Normal sq. epithelium stains mahogany brown.

5. Atypical vessels

Focal colposcopic abnormality where blood vessels appear as irregular with marked variation in caliber and with bizarre branching like commas, corkscrew patterns, spaghetti like appearance which is suggestive of early invasive cancer.

Colposcopically suspect invasive cancer

This is not evident on clinical examination. The lesion is usually raised with irregular surface contour, abnormal vessels, dense AW change, wide irregular and coarse punctate or mosaic pattern of vessels.

Unsatisfactory Colposcopy

When squamocolumnar junction is invisible or when there is severe inflammation or atrophy or when the cervix is not visible, it is called as an unsatisfactory Colposcopy.

Miscellaneous findings

1. **Non AW micropapillary surface** – is associated with congenital normal development, inflammation and chemical irritants.
2. **Exophytic condyloma** – It is seen in HPV which occurs either inside / outside the TZ. Surface is micropapillary or microconvulated AW areas may be flat or dense and irregular vessels may be present.
3. **Inflammation (Vaginocervicitis)** – Diffuse pattern of hyperemia, characterized by alterations in capillaries that may be coiled, dialated or duplicated. Occur like punctate like, mosaic like patterns as seen in trichomoniasis. More marked inflammation produces yellow spots due to lymphocyte collection, white spots (reverse punctuation), minute papillae (Micropapillary cervicitis). No change on acetic acid application Iodine staining produces partial uptake. Extension to vagina is common (Coppleson).
4. **Atrophy :** Thin estrogen deprived epithelium which is prone to bleed upon introducing speculum in the form of petechae usually reversed by estrogen therapy.
5. **Ulcers :** Denuded surface epithelium and stroma due to trauma, chemicals or microorganisms.
6. **Erosion :** Denuded surface epithelium only due to trauma or acidity. Edges are of normal appearance.
7. **Polyp :** Appearance is characteristic of columnar epithelium or typical or atypical TZ or their combinations. Malignant polyps arising from endocervical canal may show AW epithelium and vascular abnormalities.
8. **Deciduosis :** Change during pregnancy in which stroma becomes edematous and hyperplastic.
9. **Leucoplakia :** White epithelium, that is present before the application of acetic acid. It is a focal colposcopic lesion in which hyperkeratosis or parakeratosis is present. It is identified both inside or outside TZ.

1. **Coppleson's Schema (1960) :** Coppleson and co – workers formed a grading system to help to predict the underlying histology. This system is found to be practical, simple and useful.

Grade I : Insignificant, Not suspicious, Flat, Semitransparent AW epithelium with indistinct borders with fine caliber regularly shaped vessels. The predicted histology is metaplastic epithelium, acanthotic epithelium, SPI and CIN I.

Grade II : Significant, Suspicious Flat AW epithelium of greater opacity with sharp borders. Surface capillaries are regularly shaped,with defined patterns, absence of atypical vessels ; usually with increased intercapillary distance.

The predicted histology is CIN 2 –3 (HSIL).

Grade III : Highly Significant, Highly suspicious, represents very opaque, gray white epithelium with sharp border. Surface capillaries appear dialated and are irregularly shaped with increased but variable intercapillary distance.
The predicted histology is CIN 3 (HSIL) or early invasive cancer.

2. Reid's Combined Colposcopic Index : Reid and Scalzi proposed a scoring system to predict the histologic diagnosis on the basis of 4 features which include, margin, colour after acetic acid application, vessels and iodine uptake. Combining the 4 features, the combined colposcopic index was 97% accurate in forecasting SPI or LSIL and HSIL

Colposcopic	**Zero point**	**1 Point**	**2 points**

sign			
1. Margin	✸ Condylomatous or micropapillary contour ✸ Indistinct AW ✸ Feathered margins ✸ Satellite lesions and AW that extends beyond TZ ✸ Angular lesions	Regular lesions with smooth straight outlines	✸ Rolled, peeling edges ✸ Internal demarcation between two areas of differing appearance
2. Colour	✸ Shiny, snow white ✸ Indistinct AW	Intermediate grade (shiny gray)	Dull, oyster white
3. Vessels	Fine – caliber vessels, poorly formed pattern	Absent surface vessels after acetic acid application	Definite punctation or Mosaicism
4.Iodine staining reaction	✸ Positive iodine staining ✸ Minor iodine negativity	Partial iodine negativity	Negative staining of significant lesion

Interpretation of scores

0-2 = SPI or CIN I

3-5 = CIN I – II

6-8 = CIN II-III

3. Other grading systems are

a) Stafl schema

b) Burke's grading system

Modified forms of Colposcopy

Telecolposcopy

A video colposcope is used to record video clips which were subsequently transmitted to a specialist for interpretation. This is used to develop a secondary screening technique for use in primary care. Sensitivity and specificity of adequate images are transmitted are 89% and 93% respectively.

Digital Colposcopy

Real time or downloaded for later review. Additionally, the image may be subsequently modified which may enhance visualization of potential abnormality, to allow measurement of lesion.

Microcolposcopy

Magnification of 100 to 300 times is used to look the structures at ultra structural level.

Microcolpohysteroscopy

In 1984, Soutler and associates reported the use of Microcolpohysteroscopy to define the extent of endocervical involvement of CIN when the upper limit of lesion could not be seen at colposcopy.

Other screening modalities

1. VIA

Speculum examination of cervix after application of 5% acetic acid also called as VIA – Visual inspection after acetic acid application. In low grade CIN, acetic acid has to penetrate into lower 1/3 of epithelium, hence AW is delayed and less intense due to lower amount of nucleoprotein. In high grade CIN and invasive lesion, AW areas are dense and opaque and they turn AW immediately after acetic acid application due to the presence of large number

of dysplastic cells in the superficial layer of epithelium and increased amount of abnormal nuclear protein.

- ★ VIAM – Visual inspection after acetic acid application with 2.5x magnification.
- ★ VILI – Visual Inspection after Lugol's iodine application
- ★ Speculoscopy – Done with 4.6x magnification.

2. Cervicography

Developed by Adolf Stafl. High quality photograph of cervix after acetic acid application is taken with a special camera and the results are sent to trained interpreters. The main advantage is that, relatively uneducated, unsophisticated health workers can be trained to take the picture of cervix and these images can be read by experts.

Interpretations:-

Negative

- ✸ Squamous junction and TZ are fully visible
- ✸ Squamous junction not fully visible, components of TZ are visible.
- ✸ Squamous junction and TZ not visible.

Atypical

- ✸ AW lesion outside the TZ
- ✸ Atypical immature squamous metaplasia
- ✸ AW Lesion inside TZ of doubtful significance

Positive

- ✸ Minor grade lesion
- ✸ Major grade lesion
- ✸ Exclude carcinoma

3. Polar probe (Truscan)

Portable optical electronic instrument that detects the existence of precancer or cervical cancer by measuring voltage decay and the scattering of various wavelengths of light. 99% of invasive CA, 90% of high grade CIN, 85% of low grade CIN were detected by polar probe. Normal finding of squamous epithelium were correctly diagnosed in 94% of patients.

4. HPV DNA Testing - Hybrid Capture technique

It is useful in women with smears reported as ASCUS to identify the patients at high risk for HSIL or invasive cancer. The specimen is combined with a base solution that disrupts the virus and releases DNA which combines with RNA probes forming the RNA-DNA hybrid which is captured on a solid phase coated with the universal capture antibodies. These antibodies are coated with alkaline phosphatase (AKP) which is detected following cleavage of the chemical dioxetene substrate that produces light and is then measured with the luminometer in retative light units (RLU).

"Reflex HPV DNA testing" has been introduced in order to avoid the inconvenience of a subsequent visit for repeat cytological testing of HPV DNA detection. This test involves, automatically testing the residual cells in liquid based cytology specimen for HPV – DNA whenever a cytological report of ASC-US is obtained. PCR is the gold standard test for HPV detection.

Cervical biopsy

Gold standard confirmatory test. Different types of biopsy methods are done which include punch biopsy, Loop excision biopsy and conisation biopsy. Punch biopsy is the most

commonly practiced method but it tends to crush and may not include stroma. A low voltage diathermy loop biopsy requires more sophisticated equipment but can control haemorrhage and produces samples of greater size. Prendiville et al have shown that, the artefactual damage is minimal and a larger biopsy can be taken for the diagnosis of microinvasion or invasion.

Endocervical curettage is done in patients with unsatisfactory colposcopy where the TZ is not fully visible to exclude glandular or squamous metaplasia or carcinoma. If adeno CA or a skip lesion is suspected, a large cone biopsy is indicated in any case.

Site of Biopsy

When the acetowhite lesion is homogenous, the site should be in the region of the new SCJ which is the most likely area to harbor the worst abnormality. However when the lesion is heterogeneous, the most suspicious area should be biopsied. In case of larger lesion, more than one biopsy can be taken. Majority of biopsies are performed in outpatients. In postmenopausal women, where the cervix is atrophic it must be performed under anaesthesia.

Richart's HPE Classification (1967) of CIN

CIN I

The undifferentiated cells are confined to the lower 1/3 of the epithelium. Nuclei are dense hyperchromatic and often retracted. Large number of binuclear cells are seen. Normal maturation seen in upper 2/3 of cervical epithelium.

CIN II

Deeper ½ or 50% of epithelial cells are undifferentiated. Nuclear abnormalities are

more marked. Nuclei are hyperchromatic, often elongated, perpendicular to surface. Superficial cells show signs of maturation. Maturation progresses from middle portion to the surface.

CIN III

Whole thickness except for few superficial layers are undifferentiated nuclear abnormalities are marked with numerous mitoses at all levels.

CIS

Carcinoma insitu indicates whole thickness of epithelial cells become undifferentiated.

Screening Intervals

ACS – American Cancer Society 2002 guidelines

1. **Age to initiate screening** : Three years after the onset of sexual activity, not later than the age 21.

2. **Screening frequency** : Annually with conventional cytology or every 2 years with liquid based cytology. After the age of 30, women with 3 consequetive normal tests may be screened every 2-3 years.

3. **Screening after hysterectomy** : No cytologic testing after total hysterectomy for benign conditions.

4. **Discontinuation** : After the age 70

5. **Routine screening for HPV infection** : Not yet FDA approved. If approved, conventional or liquid based cytology combined with test for DNA from high risk HPV

types should be performed not more often than every 3 years.

Management of CIN

1. Management of Low grade CIN (CIN I)

a) **Expectant Management** :- As 60% of CIN I lesions regress spontaneously, observation and prospective follow up, in the patient willing to come for regular follow up. The follow up is done with any of following methods :-

   a. Cytology
   b. Colposcopy
   c. Cervicography
   d. HPV DNA detection and typing

These patients should have repeat assessments at 4 to 6 monthly intervals. The patient can exit the surveillance program once three negative cytological smears are obtained.

b) **Active management** :- It is indicated if

   a. The patient will not adhere to close follow up.
   b. Lesion persists for one year.
   c. Association with high risk HPV is documented.
   d. HIV infected patients.
   e. The patient requests treatment

Ablative techniques for treating CIN

Prerequisites

i) The entire lesion is visualised within the TZ.

ii) There is no suspicion of microinvasive or invasive cancer.

iii) There is no suspicion of endocervical glandular disease.

iv) The cytology and histology should correspond

v) A high degree of clinical expertise

vi) The patient should be complaint with follow up for atleast three years.

Timing – performed in the postmenstrual period under colposcopic guidance.

Types

1. **Cryotherapy** – Rapid freezing causes crystallization of cell water leading to cell dehydration that causes increase in the concentration of intracellular salts and release of lysosomal enzymes which cause disruption of cell membranes and organelles. Freeze – thaw – freeze technique is used. CO_2 at -60^0c and N_2O at -89^0c are the gases used. Depth of tissue destruction is around 4-5 mm. No anaesthesia is required. Complications like uterine cramping, profuse watery discharge, slight spotting may last for 2-3 weeks. Cure rate of 99% achieved.

2. **Electrocoagulation diathermy (Electrodiathermy)** – This destroys tissue by a combination of fulguration and coagulation. Done under general anaesthesia. Temperatures > 70^0c are produced making this painful. Discharge and bleeding may occur postoperatively. Depth of tissue destruction is atleast 7 mm and cure rate of 88-97% are quoted.

3. **Electro coagulation** – Here, the tissue is destroyed by the application of a

thermasound heated to 120^0c to the cervical surface. Treatments of approximately 20 seconds are given to five overlapping areas. Local anaesthesia is required. Cure rate of 94% may be achieved.

4. **Laser vaporization** – Laser energy boils intracellular water, producing steam and exploding the cell CO_2 laser is most commonly used. Energy density of 20-25 W, power density of 500-1200 w/cm^2 and a beam spot diameter of 1.5 to 2 mm. is used. Depth of destruction achieved is 6-7 mm and procedure is completed in 15-20 minutes. Advantages are ; depth and extent of tissue destruction can be accurately controlled, rapid healing of margins, minimal bleeding and discharge and TZ will be visualised during follow up.

Management of high grade CIN (CIN 2 and CIN 3)

Exicisonal techniques are preferred. Types of exicisional procedures are:-

1. **Conisation** – Cold knife conisation
2. **LLETZ** – Large loop electro surgical exicision of transformation zone

Indications :-

i) Unsatisfactory colposcopy

ii) Suspected invasion on cytology, colposcopy or biopsy

iii) Endocervical curettage is positive

iv) Lack of correlation between cytology, colposcopy and biopsy

v) Suspected adenocarcinoma

Types of cones – shallow cones where lesion is visible and columnar epithelium is also visible in the cervical canal.

Deep cones when the apex of lesion is in the cervical canal and part of lesion is out of

sight. Not performed in woman, desirous of future childbearing.

		Cold knife conisation	Laser conisation
1.	Admission and anaesthesia	Needed and GA	Office procedure LA
2.	Colposcope	Not used	Used
3.	Healing process	Slow	Rapid
4.	Scarring and Stenosis	Present 26-36%	Rare 7%
5.	Visibility of new SCJ	No	Yes

Depth of tissue destruction in laser conisation is 7-8 mm. Efficacy is 96%.

LLETZ

Indications

i) High grade CIN

ii) CIN I persisting for > 12 months

iii) Glandular intraepithelial neoplasia

Contraindications

i) Extremely large lesions

ii) Vaginal extension

iii) Obvious clinical carcinoma

It is done under local anaesthesia under colposcopic guidance. The loop is advanced into the cervix just lateral to the TZ until the required depth has been achieved. It is then slowly taken across the cervix enveloping the TZ. Fine wire loops 2.5 x 2.5 cm with electrosurgical units with power output of 30 and 60 W units are used. Cure rates for small loops are 80% and for large loops are 90%. The specimen is marked at the endocervical canal margin at 12 o'clock position with a needle.

The main advantages are; Short time, less morbidity and a tissue specimen for pathological examination is available.

Hysterectomy – can be considered for the treatment of CIN in;

1. Poor compliance of followup
2. Microinvasion
3. Positive cone margins
4. Associated gynaecological problems like fibroid, prolapse

MATERIALS AND METHODS

MATERIALS AND METHODS

This study was conducted in the Department of Obstetrics and Gynaecology at Government Rajaji Hospital, Madurai in the year 2004 April to 2005 June. This was a prospective clinical study conducted in 200 women who fulfilled the selection criteria. The average number of women attending gynaecology OP at Government Rajaji Hospital was about 75-100/day. Among them women who fulfilled selection criteria were randomly selected.

The criteria to select women for study were the presence of either one or more of the factors given below.

Inclusion criteria

1. Age : 20-60 years
2. Patients with abnormal symptoms like profuse white discharge, post coital bleeding, intermenstrual bleeding or post menopausal bleeding.
3. Patients with clinically unhealthy cervix diagnosed by speculum examination like, cervical erosion, cervicovaginitis, cervical polyp, condylomas etc.
4. Patients with pap smears showing dysplasia

Exclusion criteria

1. Women with age > 60 years and < 20 years.
2. Patients with bleeding at the time of examination.
3. Women with frank invasive cancer
4. Women who underwent total hysterectomy

5. Pregnant women

Materials

1. Colposcope :- Simple colposcope with magnifications 5X, 10X and 20X with inbuilt green filter was used. The magnification can be altered by changing the power of the eyepieces.

Magnifications of 7.5X to 10X was preferred which was excellent for localizing or zooming in the area of interest and for examining the angio architecture. The best focal distance was between 250 mm and 300mm. This allowed easy working and manipulation of instruments without hampering the vision.

2. Basic colposcope tray containing:-

- Cotton swabs with small cotton tipped applicators
- Cusco's self retaining bivalvular speculum
- Normal saline
- 5% acetic acid
- Lugol's Iodine
- Ayre's spatula
- Slide, coverslips
- 95% ethanol
- Cervical punch biopsy forceps
- 10% formalin
- Monsel's paste

3. Light microscope

Methods :- Basic steps of examination include;

1. Written informed consent and counselling
2. History
3. Physical examination
4. Local examination of vulva
5. Speculum examination of cervix and vagina
6. Pap smear – Conventional method using Ayre's spatula and fixed using 95% alcohol
7. Smears – Wet film preparation for examination of Trichomonas vaginalis and 10% KOH staining for candida examination
8. Normal saline colposcopy
9. Inspection of cervix after application of 5% acetic acid
10. Examination through green filter
11. Staining the cervix with Lugol's iodine
12. Colposcope directed biopsy using a cervical punch biopsy forceps
13. Application of Monsel's paste for hemostasis
14. Recording findings in Odell's diagram Colpophotographs were taken in necessary cases.

1. Colposcopic examination of unstained cervix

Cervix was examined under illumination after cleaning the vagina and cervix with cotton swabs dipped in NS in order to remove the discharge.

2. Inspection of cervix after 5% acetic acid application

Acetic acid is a mucolytic; changes the colour of cervix after an interval of 10-30 secs. Effect was transitory and faded away in 30-40 secs. Repeated application were required throughout the procedure. The speed with which the colour change occur and the speed with which it disappeared was indicative of the degree of underlying lesion. Low grade CIN showed a shiny white, mother of pearl hue whereas High grade CIN usually appeared dull gray, opaque or oyster white. The whole TZ must be visualised.

Surface contour, margin of lesion and appearance of blood vessels were noted and documented. Grading of abnormal colposcopic findings was done using Coppleson's grade which was simple and practical.

3. Inspection with green filter

Vascular pattern of cervix appeared as black patterns when visualised through green filter.

4. Lugol's iodine application

Cervix was painted with Lugol's iodine in a 50% dilution. Mahogany Brown staining occur in glycogen rich epithelium and therefore an acetowhite area which was stained brown should indicate mature metaplastic epithelium.

Iodine negative areas were due to inflammation, columnar epithelium, immature metaplasia thin regenerating epithelium, atropic epithelium, and HSIL.

Partial Iodine uptake was seen in immature metaplasia, regenerating epithelium, SPI and LSIL "Leopord Skin" appearance was seen in infection with Candida and trichomoniasis. Test was non specific but facilitated identification of the exact site of

biopsy and to do subsequent conisation.

5. **Colposcopy directed biopsy** : Taken from the abnormal site. When the aceto white lesion was homogenous, a site near the new SCJ was selected as it was more likely to harbour the worst abnormality. In heterogenous AW lesion, the most suspicious area was biopsied. In cases where the new SCJ was not visualised fully as in post menopausal women, endocervical curettage was done. The specimen was preserved in 10% formalin, labelled and sent for HPE examination.

6. Clear documentation of findings in Odell's diagram was done.

When the patients present with severe inflammatory changes, wet film and 10% KOH staining was done to rule out Trichomoniasis / Candidiasis and the patient was treated accordingly for infection and rescheduled for colposcopic examination in next cycle.

All 200 patients underwent colposcopic examination, pap smear and Colposcopy directed biopsy.

ANALYSIS OF RESULTS

ANALYSIS OF RESULTS

1. Age Distribution

Age	Total cases (n=200)		CIN cases (n=34)	
	No.	%	No	%
20-29	26	13	1	3.8
30-39	76	38	13	17.1
40-49	62	31	12	19.4
50-60	36	18	8	22.2
Mean	39.78		41.71	

Among the 200 women, 13% (26/200) were between 20-29 years, 76 women were between 30-39 years, 31% (62/200) women belonged to the age group of 40-49 years and 18% (36/200) were between 50-60 years.

Incidence of CIN was 3.8% in 20-29 age group, 17.1% in 30-39 age group, 19.4% in 40-49 age group and 22.2% in 50 years and above. As age increased, incidence also increased. Incidence of CIN was found to be high among the age group 30-49 years.

2. Educational status

Education	Total cases (n=200)		CIN cases (n=34)	
	No.	%	No	%
Illiterate	64	32	22	34.4
1-10th std	108	54	11	10.2
+1,+2,degree	28	14	1	3.6

Among the 200 women studied, 32% (64) were illiterates, 54% (108) had primary / high school education and 14% (28) of women had higher education.

Among the illiterates, 34.4% had CIN, but among those studied upto 10th standard, the incidence was only 10.2% and among those with higher education, it was only 3.6%.

This showed a higher incidence of CIN among the illiterates than the literates.

3. Socio – economic status

Income Rs per month	Total cases (n=200)		CIN cases (n=34)	
	No.	%	No	%
< 1000	154	77	30	19.5
1001-1500	32	16	4	12.5
1501-2000	14	7	-	-
2000-3000	-	-	-	-

Majority (77%) of women belonged to low income group. (<1000 Rs. per month)

Women with monthly income of less than thousand rupees had an incidence rate of 19.5% but among women of Rs. 1001-2000 monthly income levels, it was 12.5% and among those with higher income, it was nil.

4. Multiple Sex partners

	Total cases (n=200)		CIN cases (n=34)	
	No.	**%**	**No.**	**%**
Wife	4	2	1	25
Husband	6	3	-	-

Among the study group, 2% of women had contact with more than one partner, out of them 25%(1 out of 4) had CIN. 3% (6/200) of husbands of women in the study group had history of promiscuity. Out of them, no women had CIN.

5. Duration of marriage

Duration of marriage	Total cases (n=200)		CIN cases (n=34)	
	No.	**%**	**No.**	**%**
< 5 yrs	26	13	1	3.8
5-10 yrs	70	35	5	7.1
11-20 yrs	64	32	15	23.4
> 20 yrs	40	20	13	32.5
Mean	14.99		19.35	

Among the 200 women studied, 13% (26) were married for < 5 years, 35% (70) were married for 5-10 years, 32% (64)were married for 11-20 years, 20% (40)were married for

>20 years.

The incidence of CIN was 3.8% in women with less than 5 years of married life, 7.1% for those with 5-10 years, 23.4% for those with 11-20 years and 32.5% for those with more than 20 years of married life.

There was high incidence of CIN, when the duration of marriage increased and hence the duration of exposure to sexual intercourse.

6. Contraception

Contraception	Total cases (n=200)		CIN cases (n=34)	
	No.	%	No.	%
Barrier	10	5	-	-
OCP	18	9	4	22.2
IUCD	35	17.5	2	5.7
Permanent	77	38.5	20	26
Nil	60	30	8	13.3

Among the 200 women studied, 5% (10/200) practiced barrier method and among them none had CIN. 9%(18) were taking OCP, among them 22.2(4/18) had CIN. 17.5% (35) of women had IUCD inserted, among them 5.7%(2/34) had CIN. 38.5%(77) were

permanently sterilized, among them 26% (20/77) had CIN. 30%(60/200) of women did not practice any form of contraception, among them 13.3% (8/60) had CIN.

7. Parity

Parity	Total Cases		CIN Cases	
	No.	%	No.	%
1	16	8	2	12.5
2	68	34	13	19.1
3	76	38	13	17.1
≥4	40	20	6	15
Mean	2.71		2.71	

Among the study group, 8% (16/200) were para 1, among them 12.5(2/16) had CIN. 34% (68/200) were para 2 and out of them 19.1% (13/68) had CIN.

38%(76/200) were para 3, among them 17.1%(13/76) had CIN. 20%(40/200) were para 4 or more, among them 15%(6/40) had CIN.

8. Complaints

Complaints	Total Cases		CIN Cases	
	No.	%	No.	%
White discharge	112	56	24	21.4
Post coital bleeding	14	7	4	28.6
Intermenstrual bleeding	22	11	3	13.6
Post menopausal bleeding	10	5	3	30
Loss of wt/appetite	10	5	-	-
Others	32	16	-	-
Total	200	100	34	17

The common complaints were; white discharge and bleeding PV, which was either post coital, intermenstrual or of post menopausal type. Out of the 56% (112/200) of patients who complained of white discharge 21.4% (24/112) had CIN. Of the 7% (14/200) who complained of post coital bleeding 28.6% (4/14) had CIN 11% (22/200) had intermenstrual bleeding, among them 13.6% (3/22) had CIN 5% (10/200) had post menopausal bleeding, out of them 30% (3/10) were diagnosed to have CIN. Other complaints included loss of weight, loss of appetite, UTI, lower abdominal pain. Among them, none had CIN.

9. Clinical appearance of cervix

Clinical appearance of cervix	Total Cases		CIN Cases	
	No.	%	No.	%
Atrophy	5	2.5	-	-
Congestion	31	15.5	4	12.9
Erosion cervix	117	58.5	20	17.1
Hypertrophy + congestion	13	6.5	4	30.8
Hypertrophy + erosion	24	12	6	25
Polyps	10	5	-	-
Total	200	100	34	17

When cervix was visualised using a speculum, the appearance were atrophy in 2.5%, hypertrophy with erosion in 12%, hypertrophy with congestion in 6.5%, Erosion cervix was found in majority (58.5%). Polyp was found among 5% of cases. Among women with erosion cervix, 17.1% (20/107) had CIN, among those with congestion alone, 12.9%(4/31) had CIN, among those with hypertrophy and congestion, 30.8% (4/13) were found to have CIN, and in those who had hypertrophy with erosion 25% (6/24) were CIN positive. All polyps were beningn.

10. Pap Smear Findings

Findings	No. of cases	%
Normal	10	5
Inflammatory atypia	160	80
Mild dysplasia	20	10
Moderate dysplasia	6	3
Severe dysplasia	4	2
Invasive cancer	-	-

Pap smear was taken for all patients. 5% (10/200) of smears were found to be normal, 80% (160/200) showed inflammatory atypia, 10% (20/200) showed mild dysplasia, 3%(6/200) showed moderate dysplasia, and 2% (4/200) showed severe dysplasia.

11. Acetic acid application

AW areas within TZ	Total Cases		CIN Cases	
	No.	%	No.	%
1. Flat AW areas with sharp margin	35	59.33	12	34.29
2. Dense, opaque AW area with sharp margin with punctate / mosaic pattern	24	40.67	22	91.7
Total	59	100	34	57.6

Flat AW areas with sharp margins within the transformation zone indicated immature metaplasia or low grade CIN

Among those with flat AW areas, 34.29%(12/35) had CIN. Among those with dense opaque AW area, 91.7% (22/24) had CIN.

12. Lugol's Iodine Application

Lugol's Iodine Application	Total Cases		CIN Cases	
	No.	%	No.	%
Positive	47	23.5	-	-
Partial positivity	93	46.5	10	10.75
Negative	60	30	24	40
Total	200	100	34	17

Mature squamous epithelium stained deep brown with Lugol's iodine, called Iodine positivity was found among 23.5% of cases. Among them none had CIN.

Iodine partial positivity was found among 46.5%. Speckled or variegated appearance within an area of slight AW change might be due to immature metaplasia, regenerating epithelium, SPI or CIN I. Yellow colour within an area of dense AW was highly suggestive of CIN II or III. Among them 10.75%(10/93) had CIN.

Iodine negativity was seen in 30%(60/200) representing columnar epithelium, atrophy, inflammation, HPV infection or CIN. Among them 40% (24/60) had CIN.

13. Colposcopic appearance of cervix

Appearance	No. of cases	%
Normal	5	2.5
Erosion cervix	62	31

Inflammatory changes	32	16
Polyps	10	5
Leucoplakia	4	2
AW areas	35	17.5
Punctate pattern	16	8
Mosaic pattern	8	4
Atypical vessels	-	-
Unsatisfactory	28	14
Total	200	100

Among the 200 cases studied, 29.5% (59/200) were diagnosed as colposcopically abnormal. Among the abnormal cases, AW areas were diagnosed in 17.5% (35/200). punctate pattern of vessels was seen in 8% (16/200) of cases and mosaic pattern of vessels was diagnosed in 4% (8/200) of women. Normal finding was present in 2.5% (5/200), Erosion cervix in 31%(62/200), inflammatory changes were seen in 16%(32/200) and polyps were diagnosed in 5%(10/200) leucoplakia was found in 2%(4/200) and unsatisfactory colposcopic finding was seen in 14%(28/100) and they all underwent endocervical curettage.

14. HPE Findings

HPE	No. of cases	%
Chronic cervicitis	92	46
Chronic cervicitis + erosion	54	27
Erosion cervix	5	2.5
Epithelial hyperplasia	5	2.5
Polyp (Beningn)	10	5
Mild dysplasia	16	8
Moderate dysplasia	10	5
Severe dysplasia	8	4

All 200 cases were subjected to colposcopically directed biopsy. Majority of cases, 46%(92/200) had chronic cervicitis, 27% (54/100) had chronic cervicitis with erosion,

2.5%(5/200) had erosion cervix, 2.5% (5/200) had epithelial hyperplasia, 10 had benign polyp, 8%(16/200) had mild dysplasia, 5%(10/200) had moderate dysplasia, 4%(8/200) had severe dysplasia.

15. Comparison of Pap smear with HPE results

Pap smears	No.	Normal		HPE							
		No.	%	Mild dysplasia		Moderate dysplasia		Severe dysplasia		Total	
				No.	%	No.	%	No.	%	No.	%
Normal / inflam. Atypia	170	146	85.9	10	5.9	8	4.7	6	3.5	24	14.1
Mild dysplasia	20	17	85	3	15	-	-	-	-	3	15
Moderate dysplasia	6	2	33.3	-	-	4	66.7	-	-	4	66.7
Severe dysplasia	4	1	25	-	-	-	-	3	75	3	75

Total dysplastic smears	30	20	66.7	3	10	4	13.3	3	10	10	33.3

Correct estimation by pap smear = 156 (78%)

Under estimation by pap smear = 20 (10%)

Over estimation by pap smear = 24 (12%)

True positive = 10

False positive = 20

True negative = 146

False negative = 24

Sensitivity = $\frac{\text{True positive}}{\text{True positive + False negative}} \times 100$

= $\frac{10}{10+24} \times 100$ = 29%

Specificity = $\frac{\text{True negative}}{\text{False positive + True negative}} \times 100$

= $\frac{146}{146+20} \times 100$ = 91%

Positive predictive value = $\frac{\text{True positive}}{\text{True positive + False positive}} \times 100$

= $\frac{10}{10+20} \times 100$ = 33%

Negative predictive value = $\frac{\text{True negative}}{\text{True negative + False negative}} \times 100$

$$= \frac{146}{146+24} \times 100 = 79\%$$

$$\text{Accuracy} = \frac{\text{True positive + True negative}}{N}$$

$$= \frac{10+146}{200} = 78\%$$

16. Colposcopic correlation with HPE Findings

Abnormal colposcopic findings	No. of cases	%	HPE			
			CIN I	CIN II	CIN III	Inv. CA
1. AW epithelium	35	59.3	10	2	-	-
2. Punctate	16	27.1	6	6	2	-
3. Mosaic	8	13.5	-	2	6	-
4. Atypical vessels	-	-	-	-	-	-
Total	59	100	16	10	8	-

17. Sensitivity and Specificity of colposcopy

Colposcopy	HPE		Total
	Positive	Negative	
Positive –59	TP – 28	FP-31	59
Negative – 138	FN-6	TN-135	141
Total	34	166	200

Sensitivity = $\frac{\text{True positive}}{\text{True positive + False negative}} \times 100$

= $\frac{28}{28+6} \times 100$ = 82%

Specificity = $\frac{\text{True negative}}{\text{False positive + True negative}} \times 100$

= $\frac{135}{135+31} \times 100$ = 81%

Positive predictive value = $\frac{\text{True positive}}{\text{True positive + False positive}} \times 100$

= $\frac{28}{} \times 100$ = 47%

28+31

Negative predictive value = $\frac{\text{True negative}}{\text{True negative + False negative}} \times 100$

= $\frac{135}{135+6} \times 100$ = 96%

Accuracy = $\frac{\text{True positive + True negative}}{N} \times 100$

= $\frac{28+135}{200} \times 100$ = 82%

18. Abstract

Test	True positive	False positive	True negative	False negative	Sensitivity	Specificity	PPV	NPV
Pap smear	10	20	146	24	29	91	33	79
Colposcopy	28	31	135	6	82	81	47	96

Accuracy for pap smear = 78%

Accuracy for Colposcopy = 82%

DISCUSSION

DISCUSSION

Cervical cancer was the second most frequent cancer world wide, in women after breast carcinoma. However, invasive cancer of the cervix was considered to be a preventable condition as it was associated with a long pre invasive stage (CIN) making it amenable to screening and treatment.

In the present study screening was done in 200 women with abnormal symptoms like excessive white discharge post coital bleeding, post menopausal bleeding etc, women with unhealthy cervix, and woman with dysplastic smears, with colposcopy and its results were correlated with pap smear and biopsy to determine the sensitivity and specificity of these methods in detecting CIN. Regarding age distribution, high incidence of CIN was found among the age group of 30-49 years with mean age of 41 years which was seen in 16.7% of cases. Kushtagi and Fernandes, in their study showed the prevalence of CIN was higher in women over 30 years. Vaidya showed in his study that CIN was more prevalent in the age group of >35 years. Shalini et al showed the mean age of patients with cancer cervix was 41 vs 32 in patients with benign pathology in cervix.

Regarding parity, our study showed, increased incidence of CIN among multiparous women. 19.1 % were para 2, 17.1 % were para 3 and 15% were para 4 or more.

Similar study by Shalini et al showed the mean parity was 4.2 in patients with invasive cancer. Kushtagi and Fernandez showed the prevalence of CIN was significantly higher in parity of more than 2. Vaidya showed more positive cases of CIN were found with parity more than 4. This might be attributed to hormonal and nutritional changes that occur in pregnancy, immuno suppression during pregnancy, and cervical trauma during vaginal delivery (Becker et al and Adadevoh et al).

Socio economic status had always been playing an epidemiological role in genesis of dysplasia. In our study, the incidence of CIN was found to be higher among the low income

group (19.5 %) Vaidya had showed that low socio economic status had a definite role on the development of dyskaryosis. In his study 80% of CIN I and 50% of CIN II were from the low income group. Poor personal hygiene, poor living conditions, unstable marriages, and early age at first intercourse are factors associated with both low socio economic conditions and cervical cancer.

Regarding the literacy, CIN was more prevalent among the illiterates. In our study, 64.7% (22 out of 34) of CIN was found among the illiterates. This was attributed to lack of awareness of symptoms and failure to seek medical care.

Duration of marriage and duration of exposure to sexual intercourse had a distinct role in genesis of cervical dysplasia. In our study, the incidence of CIN was 23.4 % in women who were married for 11-20 years, and 32.5% among women who were married for > 20 years. Kushtagi et al had demonstrated the severity of underlying CIN increased with increase in the duration of marital life and hence the increase in the duration of sexual intercourse.

Increasing number of sexual partners had the effect on increasing the risk of developing CIN and invasive disease. In our study, only 2% of women revealed the history of multiple sexual partners, out of which 25% had CIN.

Sex with high risk males was also another risk factor for the development of CIN. In our study, though 3% of males had multiple sexual partners, none of their wives developed CIN.

The relationship between oral contraceptives and development of CIN had been investigated by IARC – International agency for Research in Cancer and they concluded that the use of OCP increased the risk of CIN upto 4 fold after 5 or more years among the HPV DNA positive women. In our study, we found that none of the women who practised barrier contraception had CIN. Among the 9% of OCP users, almost 22.2% (4/18) showed features of CIN. Out of 17.5% of IUCD users, the incidence of CIN was 5.7% (2/35). Out of 38.5% of women who had undergone sterilization permanently the incidence of CIN was 26% (20/77).

Prospective studies by Stern et al in Los Angeles suggested an increased risk of progression of cervical dysplasia among the users of hormonal contraceptive. Vaidya et al in their study showed 40% risk of CIN I in women who had depot provera injection. According to Duggan, OCP produced progression to CIN by regulating oncogenic sequences of HPV.

Among the complaints, majority of women (56%) complained of excessive white discharge per vaginum. Among them CIN was found in 21.4% (24/112). Excessive vaginal discharge playing a role in contributing to the development of CIN was also proved to be a risk factor in the study conducted by Vaidya et al. In their study, 24% had vaginal discharge.

Post coital bleeding was found in 7% (14/200) of cases. Among them CIN was found in 28.6% (4/14). Shalini R Amita S, in their study showed the relationship of post coital bleeding and CIN. In their study, among the women who had post coital bleeding, 85.5% had beningn findings, 5.6% had HPV and CIN I, 3.6% had CIN II and III and 55% had invasive cancer. There was no correlation between the duration of bleeding and pathology.Among those with intermenstrual bleeding, 13.6% (3 out of 22) had CIN. Among those with post menopausal bleeding 30% (3/10) had CIN.

Regarding the clinical appearance of cervix, the most common finding was erosion cervix where the squamous epithelium of ectocervix was replaced by the columnar epithelium of endocervix. Erosion was seen in 58.5% (117/200), rest of patients showed congestion in 15.5%, Hypertrophy with congestion seen in 6.5%, Hypertrophy with erosion was seen in 12% and polyp was found in 5% of cases.

CIN was found in 12.9% (4/31) in women who showed congestion, 17.1% (20/117) in women who showed erosion and 30.8 % in women with hypertrophy + Congestion and 25 % in women with hypertrophy + erosion.

5% acetic acid application produces suspicious areas in 18.7% (59/200) cases. Among them, AW areas without any vascular pattern was found in 17.5% (35/200), punctate pattern

was seen in 8% (16/200) and 4% (8/200) showed mosaic pattern. Among those with AW areas, 34.29%(12/35) were found to be CIN positive.Among those with dense opaque A.W. areas, 91.7% (22 out of 24) had CIN. Londhe M, Seshadri in their study showed VIAM had a sensitivity of 72.4% and a specificity of 54% and a false negative rate of 15.2%.

Lugol's iodine application produced iodine positivity in 23.5%. Among them, none had CIN. CIN was found in 29.4% (10/34) in partial iodine positivity and 70.58% (24/34) in iodine negativity.

Pap smear was taken for all cases. It showed mild dysplasia in 10% (20/200), moderate dysplasia in 3% (6/200) and severe dysplasia in 2% (4/200). Pap smear correctly estimated CIN in 78% and underestimated in 10% and overestimated in 12% (false positivity).

Sensitivity of pap smear was found to be very low – 29% compared to its specificity which was 91%. This was attributed to the high number of false negative smears.

Sensitivity and specificity of pap smear by various authors

S.No.	Authors	Sensitivity	Specificity
1.	Londhe M, George S, Seshadri I	13.2%	96.3%
2.	Shalini R, Amita S., Neera M.A.	56%	90%
3.	Basu PS and Sankaranarayanan	29.5%	92.3%
4.	Pete I, Toth V, Bosze P	47%	77%
5.	Sukhpreet Singh	20%	91.25%
6.	Present study	29%	91%

This data suggested that with colposcopy as a screening tool, the rate of false negative cytology could be significantly reduced. Colposcopy enhanced cervical screening particularly in women with otherwise negative smears.

Correlation between cytology and HPE was poor as far as mild dysplasias were concerned. But the correlation was good for moderate and severe dysplastic lesions.

Correlation between colposcopic findings and biopsy showed a good correlation for higher grade lesions (CIN II and CIN III). Sensitivity was found to be 82% and specificity was 81%. This showed a high sensitivity and a low specificity when compared to Pap smear. Low specificity when compared to pap smear was due to the high incidence of unsuspected AW epithelium which might be due to inflammation, immature metaplasia, erosion and latent HPV infections. Out of 35 cases which showed AW areas without any vascular pattern only 10 were cofirmed by biopsy.

Sensitivity and specificity of colposcopy by various authors

S.No.	Authors	Sensitivity	Specificity
1.	Pete I, Toth V, Bosze.P	87%	15%
2.	Olaniyan B. Meta analysis	87-99%	26-87%
3.	Massad LS, Collins Y.C.	89%	52%
4.	Kier Kegaard et al	67%	-
5.	Sukhpreet L. Singh et al	95%	63.5%
6.	Present study	82%	81%

Colposcopy and biopsy were positive in 28 out of 34 (82.4%) cases while pap smear and biopsy were positive in only 10 out of 34 (29.4%) cases. This indicated the usefulness of colposcopy in diagnosing lesions missed by pap smear.

Olaniyan et al, did a meta analysis of eight longitudinal studies and compared the correlation of colposcopic impression with biopsy results. Colposcopic accuracy was found to be 89% which agreed exactly with histology in 61% of cases. In the present study, the accuracy of colposcopic impression was found to be 82%. Massad et al reported an accuracy of 80%.

Accuracy of colposcopic impression by various authors

S.No.	Author	Accuracy
1.	Olaniyan	89%
2.	Massad LS, Collins Y.C.	80%
3.	Present study	82%

Advantages and disadvantages of pap smear

Advantages

1. Ideal for mass screening
2. Economical
3. Specimen can be obtained by non medical staff
4. Detects lesions in endocervical canal
5. Detects adenocarcinoma

Disadvantages

1. Pap smear has low sensitivity
2. Value of single smear is limited
3. It cannot localize the lesion

Colposcopy

Advantages

1. Localise lesion
2. Evaluate extent of lesion
3. Differentiates between inflammatory atypia and neoplasm
4. Differentiates between invasive and non invasive lesions of cervix
5. Enables follow up

Disadvantages

1. Inadequate for detection of endocervical lesions and need endocervical curettage.
2. Needs more experience and training .
3. More costly

SUMMARY

SUMMARY

This study was a prospective study conducted in the Department of Obstetrics and Gynaecology during the period of April 2004 to June 2005 in 200 women who fulfilled the inclusion criteria. 200 women were randomly selected from the patients attending the Gynaecology OP. Colposcopy, Pap Smear and biopsy were done for all the cases after proper counselling. The results were tabulated and anayalsed. To summarize,

- Majority (73.5% i.e., 25 out of 34) of CIN occurred in the age group of 30 – 49 years.

- 38.2% (13 out of 34) with CIN were para 2, 38.2% (13 out of 34) with CIN were para 3 and 17.6% (6 out of 34)with CIN were greater than para 4 showing high incidence of CIN in multiparity.

- The incidence of CIN was found to be high among the lower income groups.(88.2% i.e., 30 out of 34)

- 64.7% (22 out of 34)of women with CIN were found to be illiterate.

- History of sexual promiscuity was present in 4 (2%) of women and among them 1 (25%) had CIN.

- 44% (15/34) of women who were married for 11-20 years and 38.3% (13/34) of women married for more than 20 years had CIN.

- Among the 18 women who took OCP, 4 (22.2%) had CIN. Incidence of CIN in the permanently sterilized group was 58.8%(20/34) and among IUCD users was

5.9%(2/34).

- Among women who were diagnosed to have CIN, 70.58% (24/34) complained of excessive vaginal discharge, 11% (4/34) of women had post coital bleeding.

- 58.5% of women among the study group had erosion cervix on speculum examination.

- Pap Smear had a sensitivity of 29% and a specificity of 91% which was attributed to the high number of false negative smears.

- PPV and NPV of pap Smear was 33% and 79% respectively. Accuracy of pap smear was 78%.

- Colposcopy showed a sensitivity of 82% and a specificity of 81%. Sensitivity was more than pap smear but specificity was less than pap smear.

- PPV and NPV of colposcopy were found to be 47% and 96% respectively.

- Accuracy of colposcopy was found to be 82% which was comparatively more than that of pap smear (78%). This accuracy was high for high grade lesions than the low grade lesions.

CONCLUSION

CONCLUSION

Earlier diagnosis of CIN in adult women is a desirable goal. CIN lesions and early invasive cancers should be diagnosed in an earlier stage for instituting appropriate management. Invasive cancer of cervix is considered to be preventable since it is associated with a long pre – invasive stage (CIN) making it amenable to screening and treatment.

From the results of this study, it is evident that colposcopy is definitely more sensitive and accurate than pap smear. By combining pap smear with colposcopy , we can maximise the sensitivity and specificity of cancer cervix screening.

Colposcope in general has a role in the evaluation of women with abnormal pap smears, unhealthy cervix, and seems to be more accurate in detecting CIN. Hence, primary colposcopy may be incorporated into genito urinary tract screening at first visit.

Thus colposcopy offers an excellent tool in evaluating cervical lesions. It is an easy and perspective method and its importance lies in teaching, diagnosis and management of cervical lesions, both neoplastic and non – neoplastic. There is a need to introduce and encourage the practice of colposcopy, in all medical institutions to evaluate and manage patients with clinically suspicious cervix and abnormal pap smears.

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BIBLIOGRAPHY

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PROFORMA

PROFORMA

Serial No. Name

IP. OP. No. Age

Income Education

I. Complaints

1. Bleeding PV
   - Post coital bleeding
   - Continuous / Intermittent
   - Intermenstrual
   - Post menopausal
   - Associated pain
2. Vaginal Discharge
   - Duration
   - Quantity
   - Colour
   - Foul smell
   - Pruritis
3. Lower abdominal pain
4. Urinary symptoms
5. Bowel symptoms
6. Loss of weight
7. Loss of appetite

II. Personal History

- ★ Diet
- ★ Hygiene

III. Menstrual History

- ★ Age at menarche
- ★ Cycles
- ★ LMP
- ★ Age at menopause

IV. Married since

V. Sexual promiscuity

- ★ Multiple sexual partners
  - Husband
  - Wife

VI. Obstetrical History

- ★ P L A
- ★ LCB
- ★ Contraception

  Barrier
  - OCP
  - IUCD
  - Permanent
  - Nil

VII. General Examination

Built	Thyroid
Anaemia	Breast
Pedal edema	BP
Lymphadenopathy	PR
CVS	RS

VIII. Per abdomen

IX. Local examination of Genitalia

- ★ Normal
- ★ Abnormal

X. Speculum Examination

- ★ Cervix
- ★ Vagina

XI . Pap Smear

XII. Colposcopic Examination → AW

→ Lugol's Iodine

XIII. Colposcopic Findings

Normal	Abnormal	Indesicive	Miscellaneous
Original Sq.epi	AW		Erosion cervix
Columnar epi	Punctate		Inflam. Changes
TZ	Mosaic		Atrophy
	Atypical vessels		Polyp
			Leucoplakia
			Condyloma

XIV. Per vaginal examination

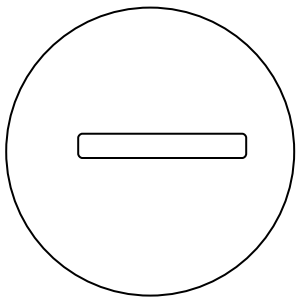
XV. P/R

XVI. Biopsy

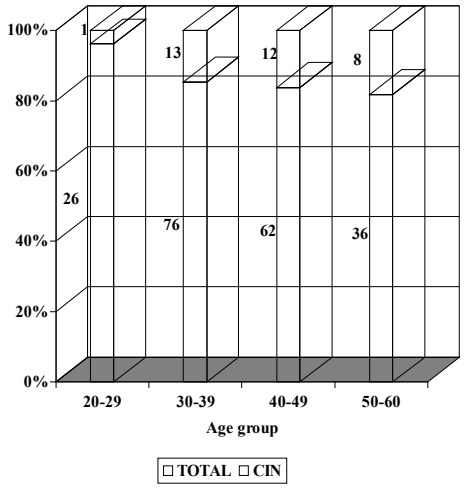
Colposcopic grading (Coppleson's method)

- ★ Surface contour
- ★ Border
- ★ AW
- ★ Vascular pattern

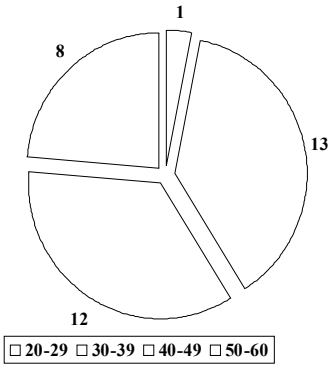
ODELL' S Diagram



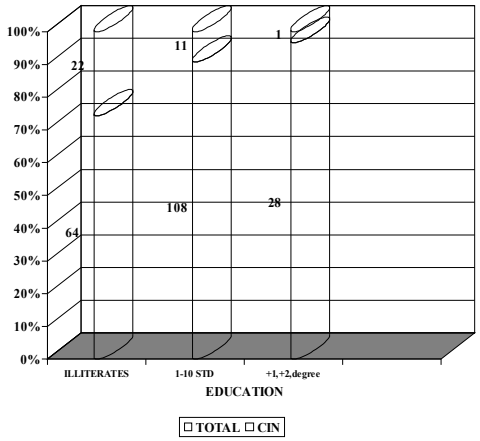
Age distribution



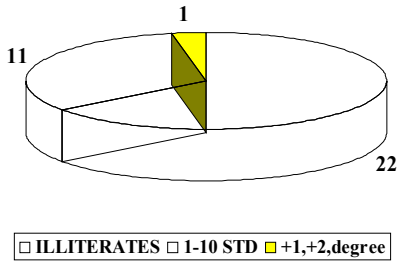
Age distribution of CIN cases



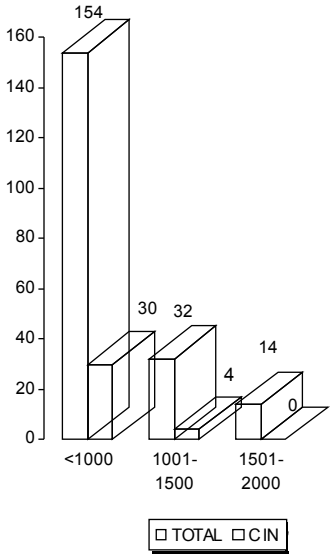
Educational status



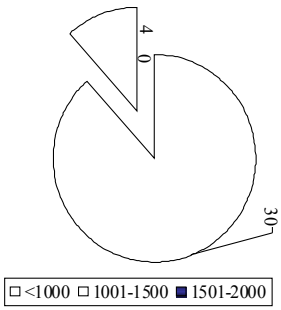
Educational status of CIN cases



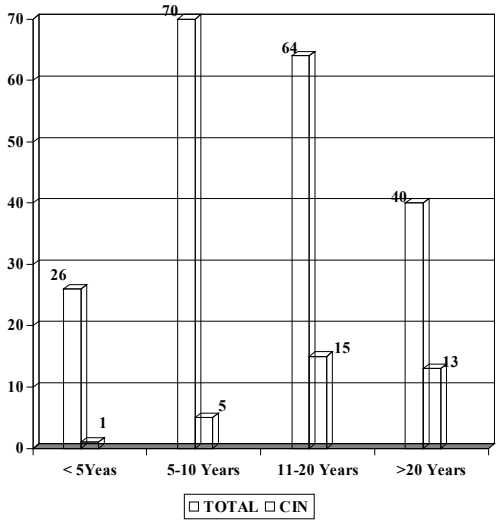
Socio economic status



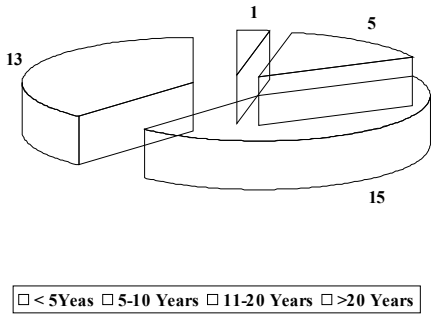
Socio economic status of CIN cases



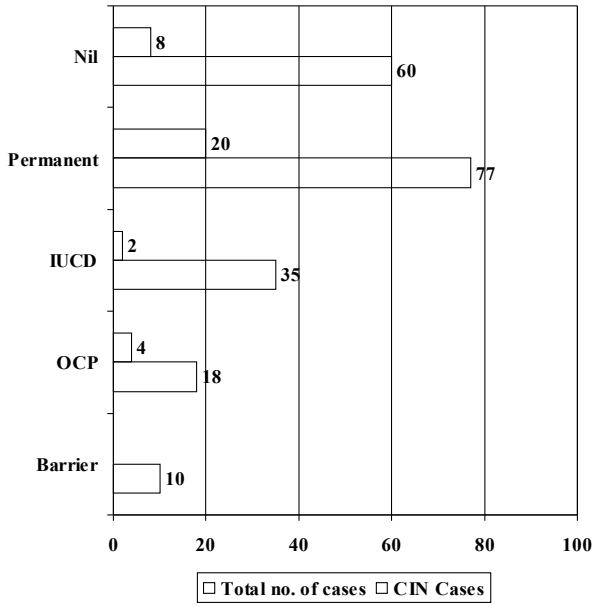
Duration of marriage



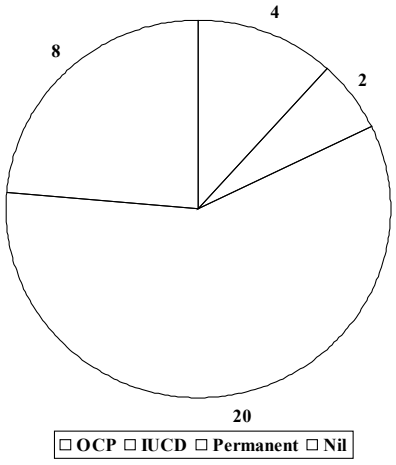
CIN Cases



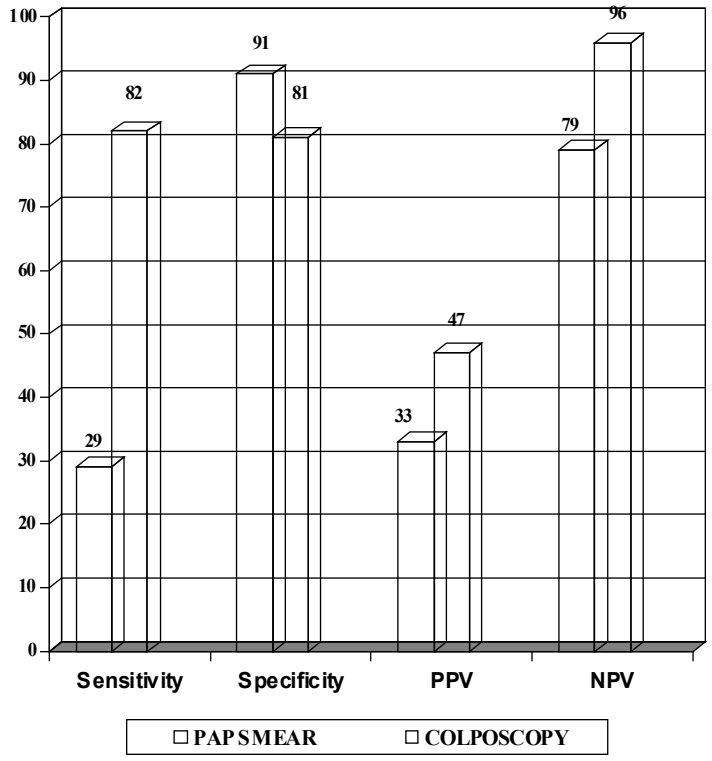
Contraception



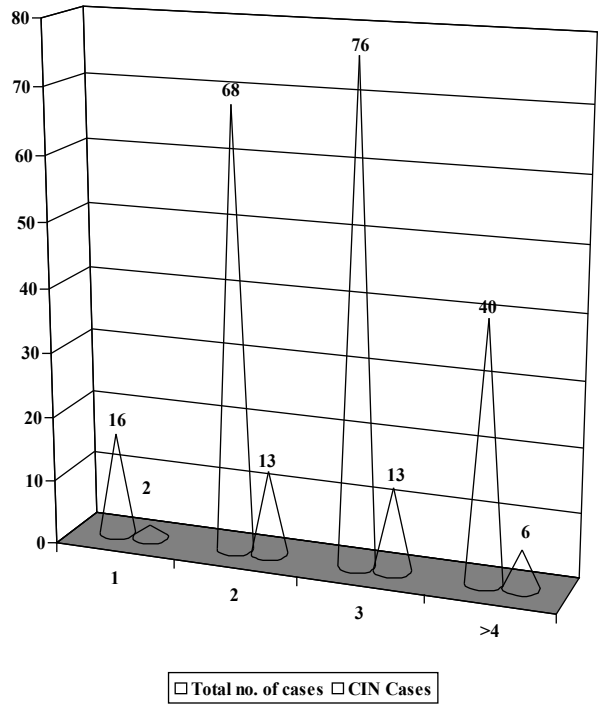
CIN Cases



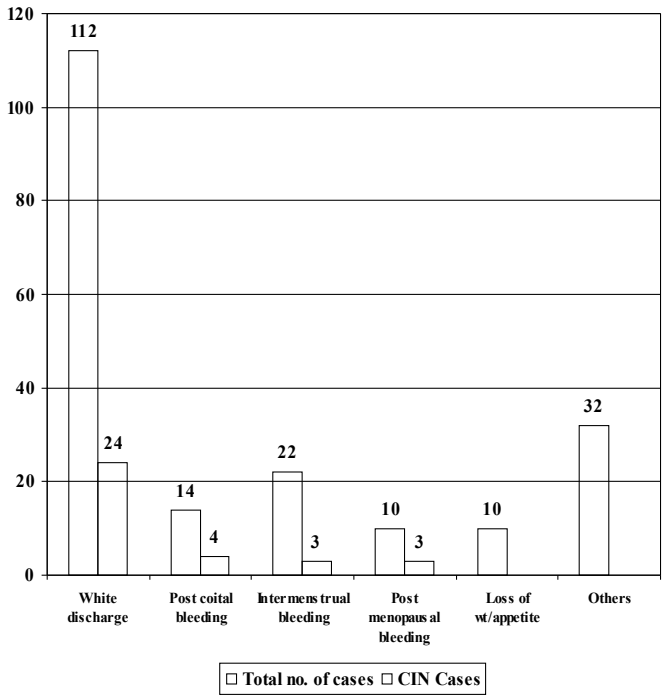
Efficacy of PAP smear and Colposcopy



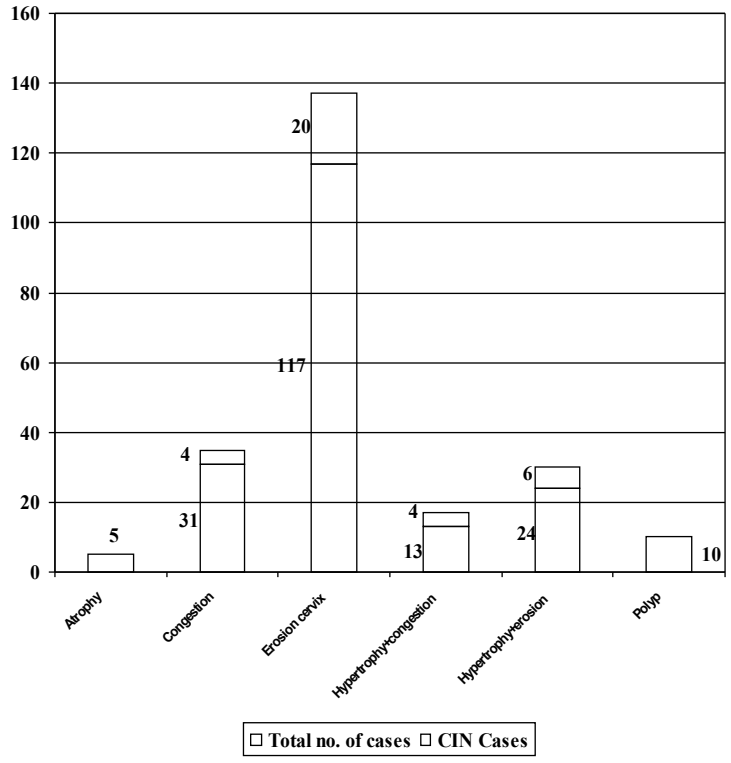
Parity


80
70
60
50
40
30
20
10
0
76
68
40
16
13
13
2
6
1
2
3
>4
Total no. of cases
CIN Cases

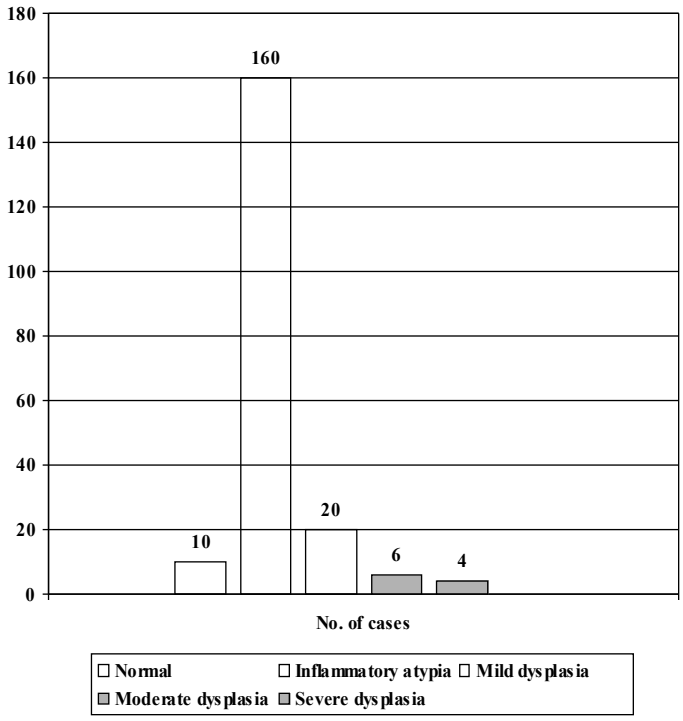
Complaints


120
100
80
60
40
20
0
112
24
14
4
22
3
10
3
10
32
White discharge
Post coital bleeding
Intermenstrual bleeding
Post menopausal bleeding
Loss of wt/appetite
Others
Total no. of cases
CIN Cases

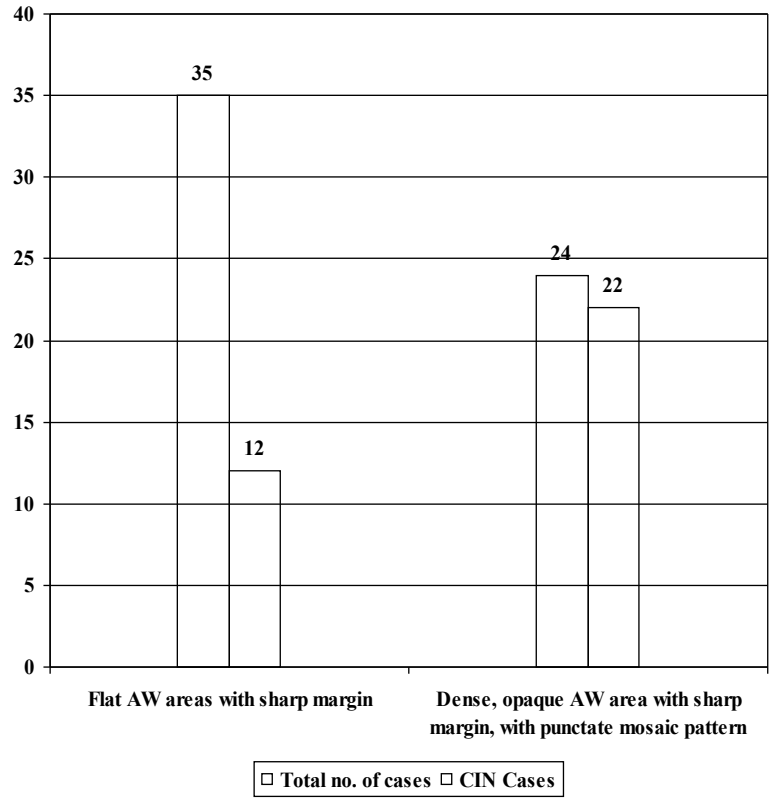
Clinical Appearance of Cervix



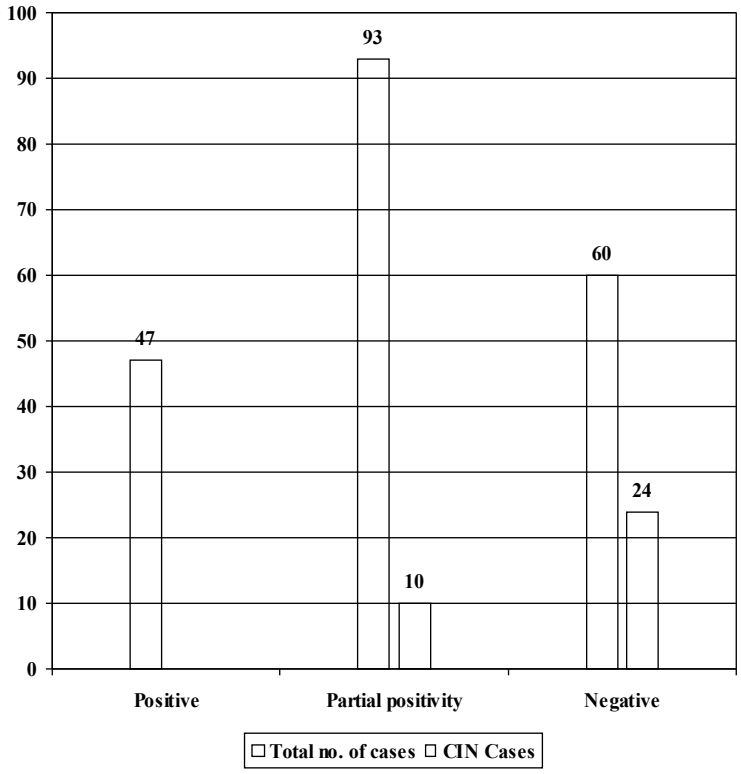
PAP Smear findings



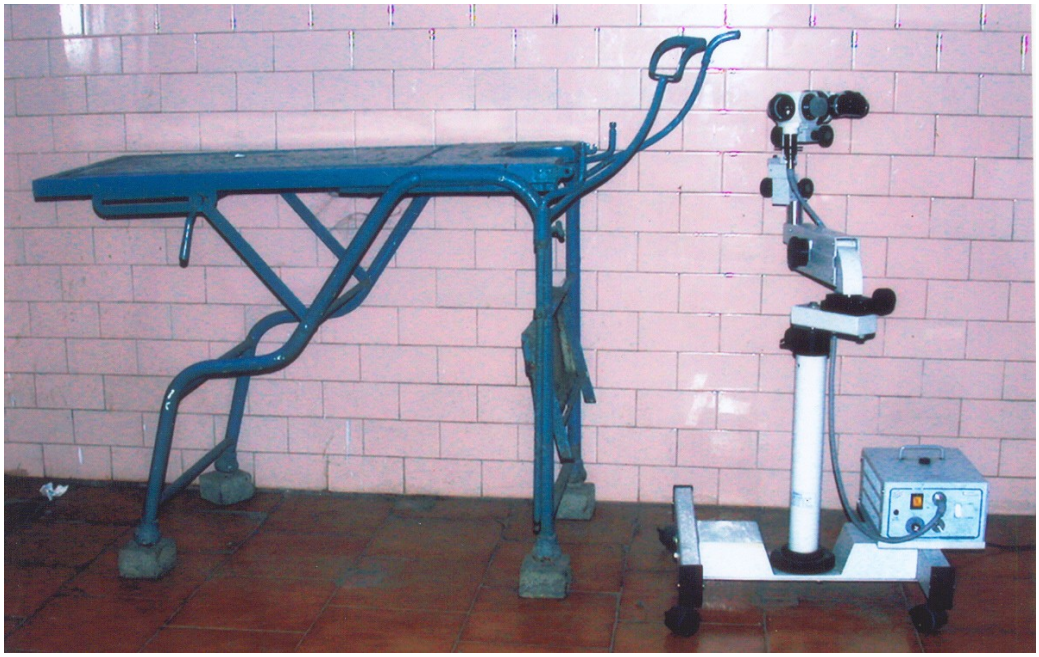
Acetic acid application



Lugol's Iodine application

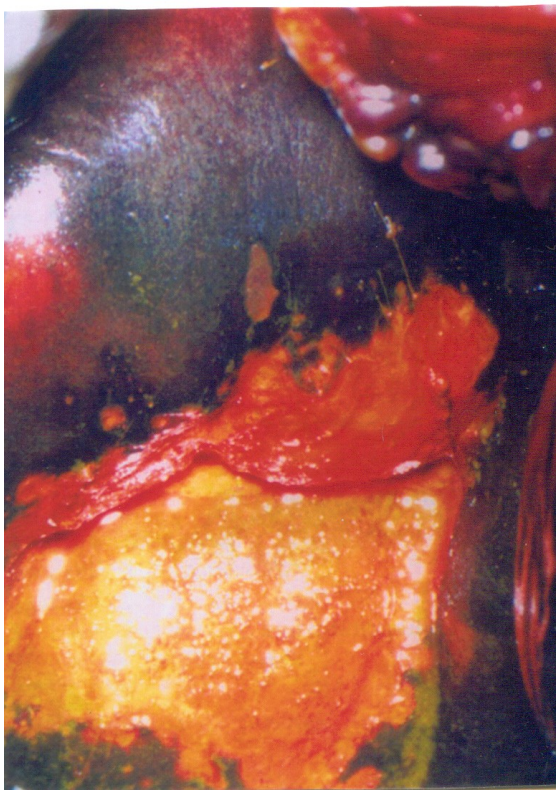


Colposcope

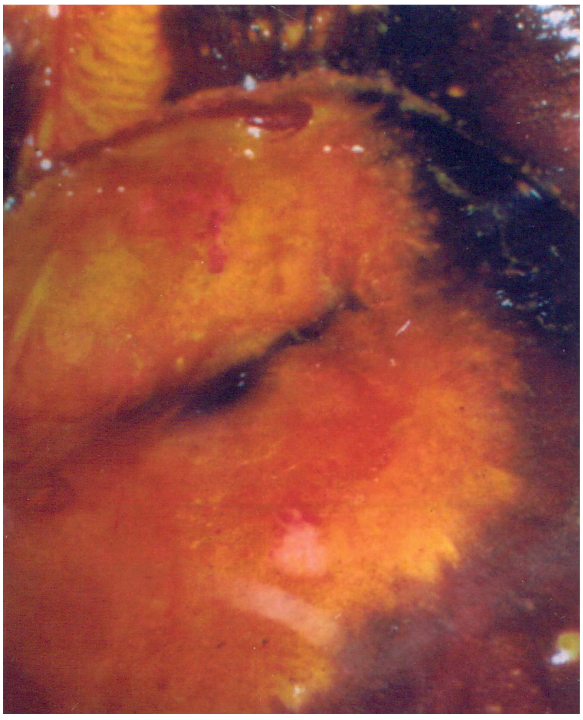


Normal colposcopic appearance

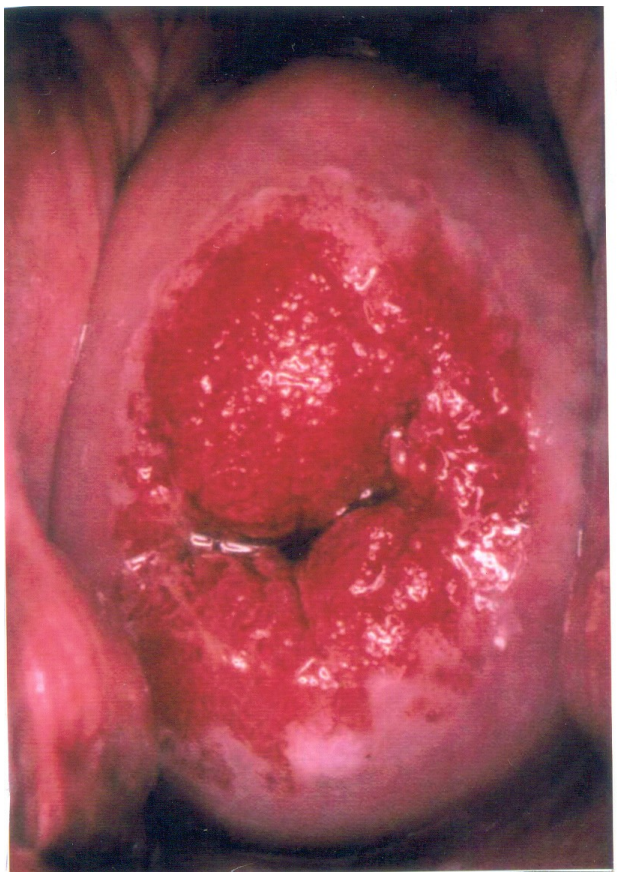
Partial Iodine Positivity



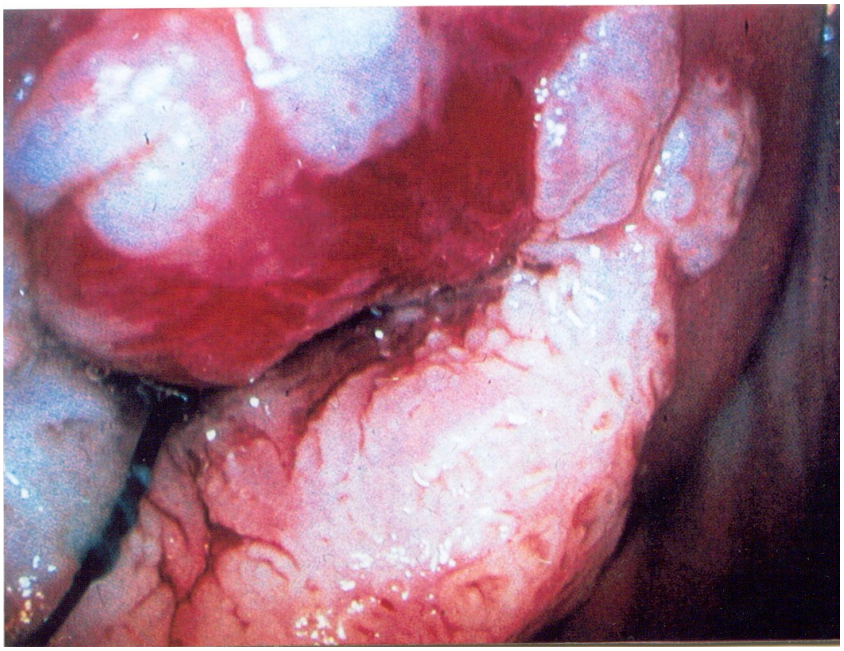
Iodine Negativity



Cervical erosion

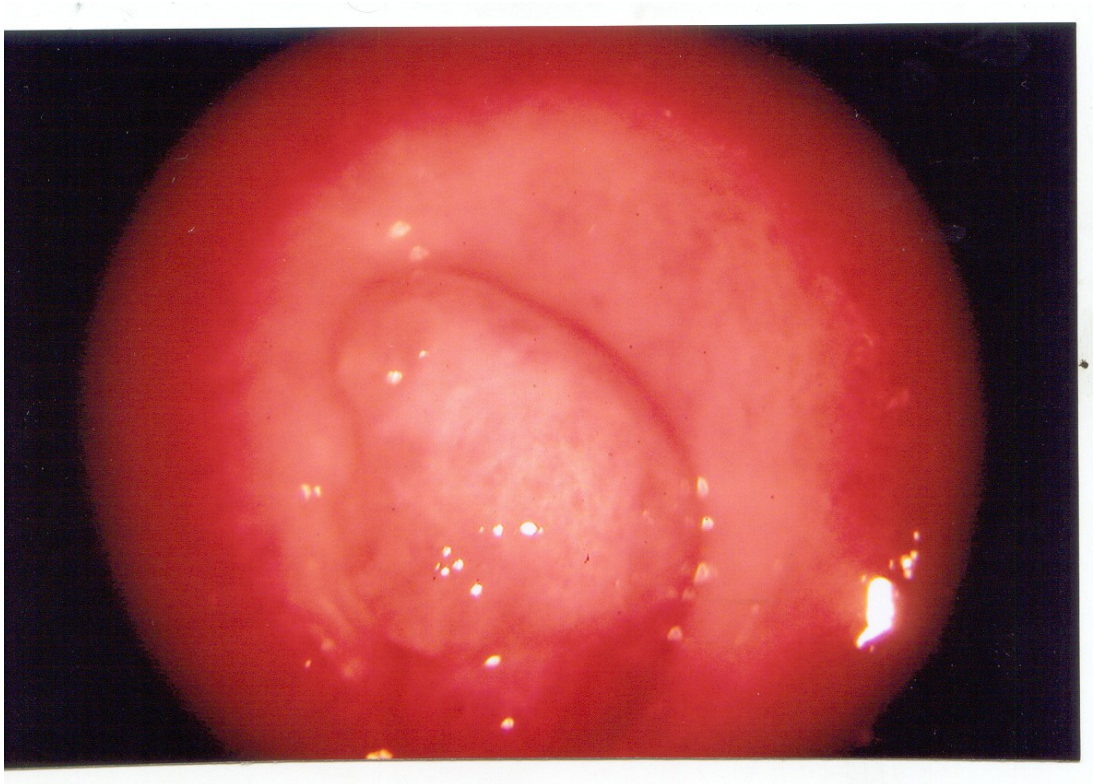


AW areas in upper and lower lips

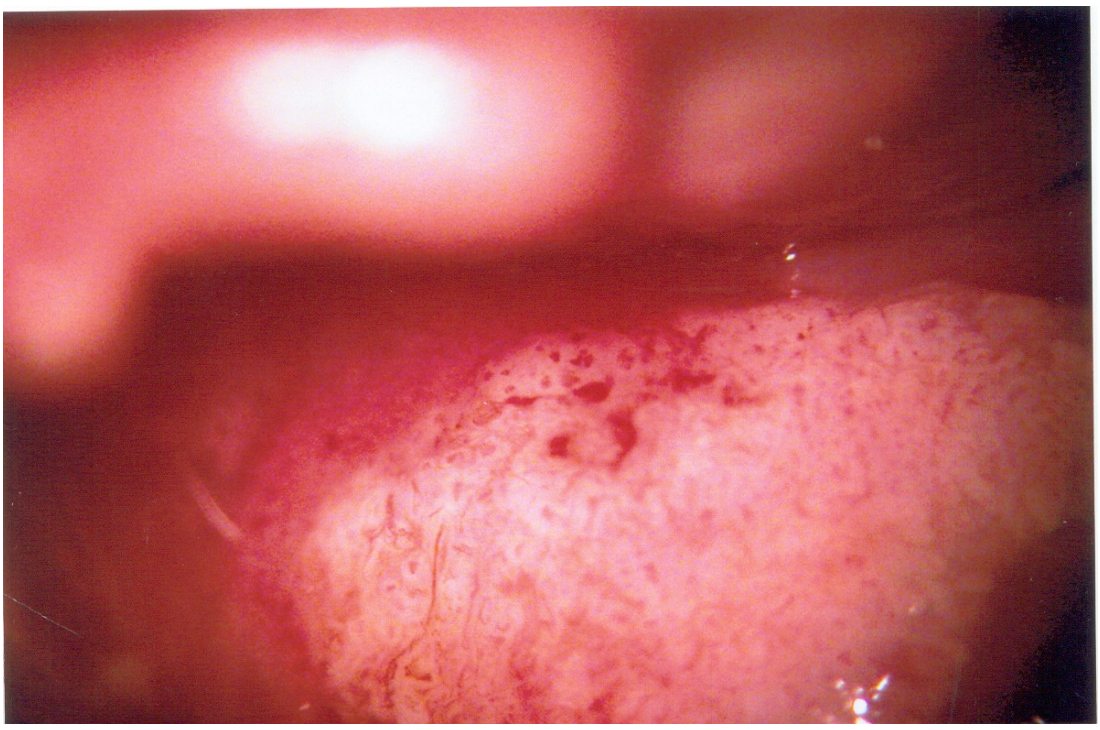


AW area (dense) at 2^{0}'clock

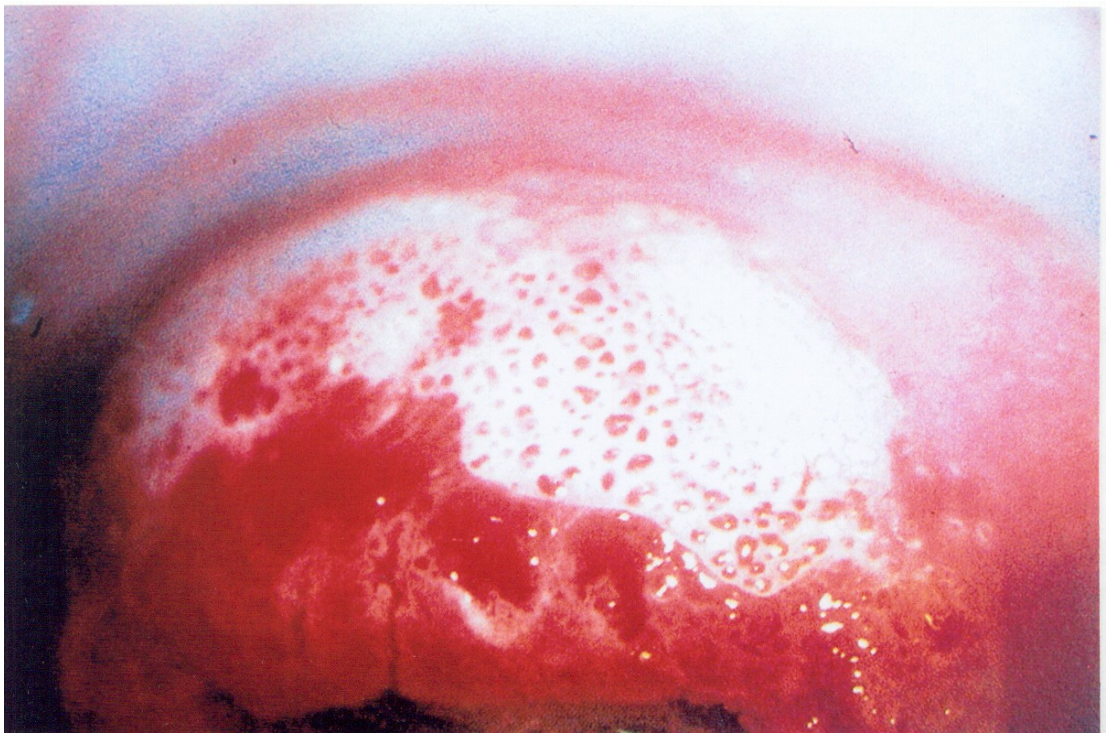
Cervical Polyp



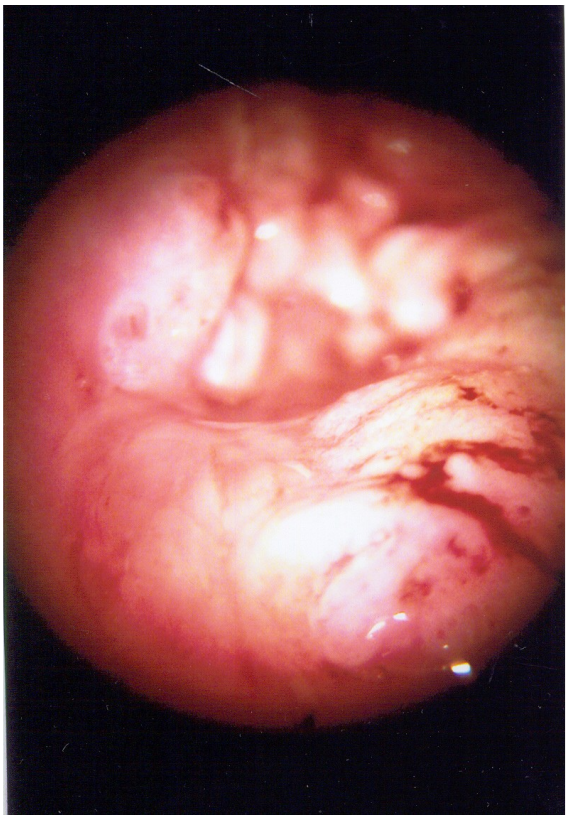
Coarse Mosaic pattern in the lower lip



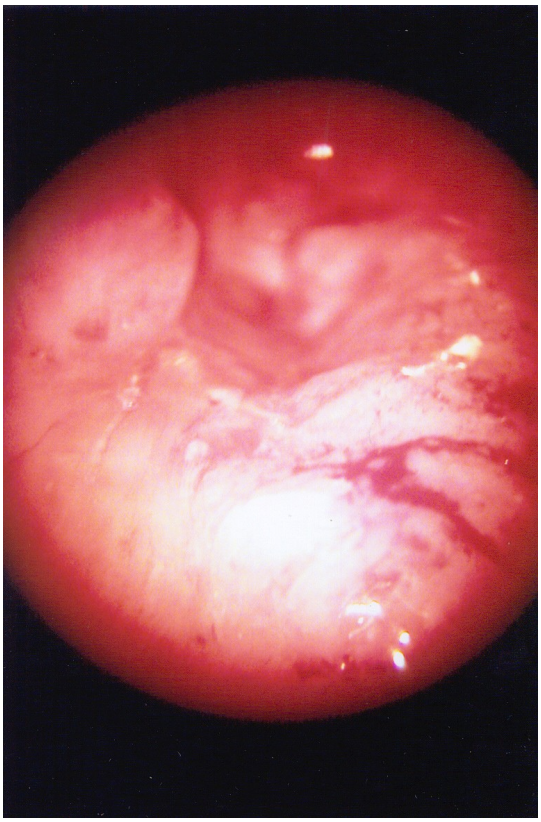
Coarse punctate pattern in upper lip of cervix



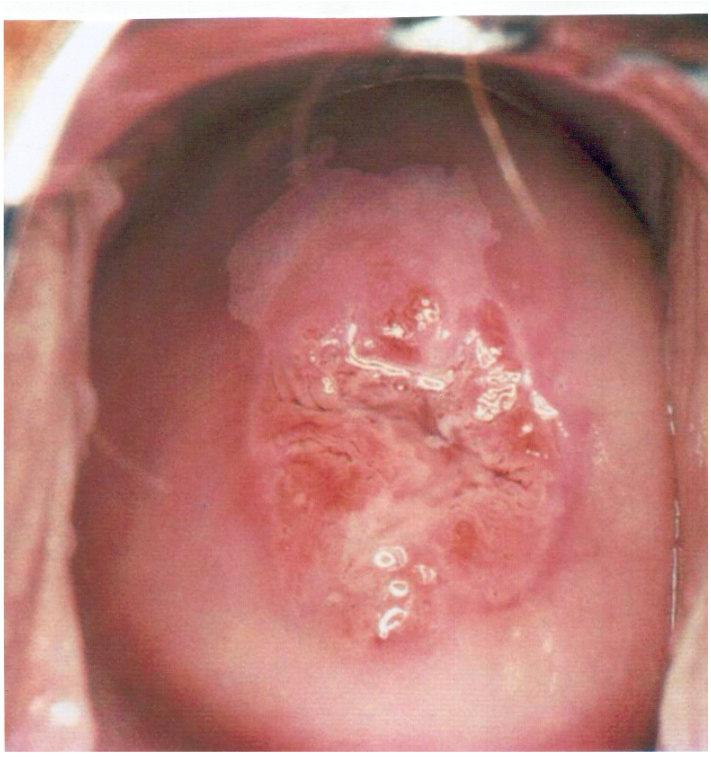
AW at 6^{0}' clock position



Punctate pattern at 4^{0}' clock



AW area at 12^{o}' clock position



Coarse mosaic pattern with satellite lesions